ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 27 (O.S., Vol. XXXI) JULY, 1947 NUMBER 1

CONTENTS

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $8.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

These pills are engaging increased interest in neurological clinics as well as in private practice, especially in the treatment of the *Sequelae of Epidemic Encephalitis.* They embrace the full therapeutic properties of the drug in a form convenient for administration.

Each pill exhibits 0.16 Gram (2½ grains) of the dried leaf and flowering top of Datura Stramonium, alkaloidally standardized, and therefore contain 0.4 mg. (1/100 grain) of the alkaloids in each pill.

Sample for clinical test and literature mailed upon request.

Davies, Rose & Company, Limited

Manufacturing Chemists, Boston 18, Massachusetts

ANNALS OF INTERNAL MEDICINE

VOLUME 27 JULY, 1947 NUMBER 1

FURTHER OBSERVATIONS ON THE TREATMENT OF TYPHUS FEVER WITH PARA-AMINO-BENZOIC ACID *

By J. C. SNYDER, M.D., A. YEOMANS, M.D., D. H. CLEMENT, M.D., E. S. MURRAY, M.D., C. J. D. ZARAFONETIS, M.D., and N. A. TIERNEY, M.D.

THE therapeutic effect of para-aminobenzoic acid (PABA) in experimental murine typhus infection of white mice was reported in 1942.[1] Subsequently, evidence bearing on the action of PABA in experimental rickettsial infections has been obtained in several laboratories. In the yolk sac membrane of developing chick embryos, PABA or its sodium salt inhibits the multiplication of *Rickettsia mooseri*,[2, 3] *R. prowazeki*,[2, 4, 5] *R. orientalis*,[5] and *Dermacentroxenus rickettsi*.[4] The mortality in experimental rickettsial infections in white mice,[1, 6] gerbilles,[7, 8, 9] cotton rats,[10] and guinea pigs[11] is considerably reduced by PABA.

In 1944 a favorable therapeutic effect from the administration of PABA to several patients who were in the first week of classical typhus fever was reported from Egypt by Yeomans et al.[12] Successful results in the treatment of 18 cases of tsutsugamushi disease with PABA were obtained by Tierney in Burma.[13] One patient suffering from Rocky Mountain spotted fever was treated by Rose, Duane, and Fischel with apparently beneficial results.[14]

It is the purpose of this paper to record additional experience in the administration of PABA to patients with epidemic louse-borne typhus fever. Part I analyzes statistically the data obtained in 1944 [12] from a series of alternate treated and control patients in Cairo, Egypt, together with new data from a similar series of the same size observed in 1945. Part II describes the treatment of 60 patients in an epidemic of typhus in a concentration camp in Germany and of a miscellaneous group of five patients. Part III states several points of importance in the administration of PABA in human rickettsial infections.

* Received for publication March 18, 1947.

From the United States of America Typhus Commission, War Department, Washington, D. C., and the Laboratories of the International Health Division of The Rockefeller Foundation, New York.

PART I

Alternate Control and PABA-Treated Typhus Fever Patients, Cairo, Egypt, 1944–1945

In 1944 it was possible to study a small group of patients who met certain criteria at the time they were admitted to the experimental ward established by the United States of America Typhus Commission in the Cairo Fever Hospital, through the courtesy of Egyptian officials.[15] These patients were placed alternately in control and PABA-treated groups. In 1945 a similar study was carried out in the same ward. Considered together, the cases of the two years can be analyzed statistically. In this report a more accurate procedure has been used to determine from the case histories the duration of illness at the time of admission to the study groups and the total duration of fever. The "clinical classification of severity," based on a review of each patient's record when he was discharged from the hospital, has been replaced by a more objective method for the evaluation of the severity of illness. For these reasons, the data on 10 patients treated in 1944, although presented previously, are included with the new data on 10 patients treated in 1945.*

Criteria for the Selection of Patients. The study groups were composed of 39 male Egyptian patients, ages 18 to 48, suffering from epidemic louse-borne typhus fever. The diagnosis was based on the clinical course, the serologic findings and, in 19 instances, the isolation of *R. prowazeki* from the blood or from normal lice fed on the patients during the febrile period, as indicated in tables 1 and 2. None of the patients had been vaccinated against typhus fever. None gave a history of a previous attack of the disease. All came from the same social stratum. Nearly all were somewhat underweight, but otherwise they appeared to be in good physical condition. At the time of admission to the Typhus Commission Ward, none had evidence of complicating illnesses or conditions. A few of the patients in both the control group and the PABA-treated group were subsequently found to have subclinical schistosomiasis, but no patients were excluded from consideration because of this finding. One of the control patients has been excluded from the analysis because he had active pulmonary tuberculosis. One PABA-treated patient developed an exacerbation of chronic amebic

* Tabulation of PABA-treated typhus cases:

First report[12]:	
7 patients treated consecutively, 1943	
3 miscellaneous cases, 1944	
10 treated patients in alternate series, 1944 (form half of group analyzed statistically in Part I, present paper)	
Present paper:	
10 treated patients in alternate series, 1945 (form other half of group analyzed statistically in Part I)	
60 patients treated at Dachau (1945)	
5 miscellaneous cases	
Total	95

dysentery during convalescence from his attack of typhus; this patient is included in the analysis.

The patients were in the first week of illness at the time of admission to the study groups. They were placed in the control and PABA-treated groups in automatic rotation. When two patients were found simultaneously, the patient having the lower hospital number was selected for the group requiring the next case. In 1944 this schedule was followed, with the two exceptions noted in an earlier report [12]; in 1945 during most of the study the automatic rotation involved three groups: (1) control; (2) PABA-treated; and (3) special high-calorie diet group. The studies of the patients on the specially supplemented diet are reported in another communication.[16]

The period of the study covered only the few weeks at the peaks of the 1944 and 1945 typhus epidemics in Cairo.

In the group which was treated with PABA all patients received the drug for more than three days in amounts adequate to produce measurable concentrations of diazotizable substances * in their blood throughout the period of therapy. The method of administering PABA in 1945 was the same as that employed in 1944,[12] except that somewhat larger doses of the drug were given and higher concentrations in the blood were attained.

All of the patients received routine nursing care, a uniform diet, and supportive measures intended to combat specific complications as they developed. Temperatures were taken rectally every four hours in the febrile period and early convalescence.

Estimation of Duration of Illness. Typhus patients who have not been sick long enough to become stuporous or delirious can usually recall the hour of the day or night when they became ill. This information was determined for 35 of the 39 patients in this study. Whenever possible, the history given by the patient was checked carefully by talking with his family and by visiting his place of employment. In four instances information from these sources was of value in fixing the time of onset of illness.

The duration of illness at the time each patient was first admitted to the study groups was estimated to the nearest quarter day on the basis of the hour of onset as stated in the history. The duration of fever was estimated in a similar manner, from the onset of illness to the last rectal temperature reading above 37.5° C. An interval of secondary fever occurred in a few of the cases in the PABA-treated group. In the analysis of the data the duration of the secondary fever has been added to that of the primary fever, the total being expressed to the nearest quarter of a day.

Estimation of Severity of Illness. In the 1944 report [12] each patient's record was reviewed at the time of his discharge from the ward, and the severity of his illness was classified in one of six groups. Although previously reduced as much as possible, the subjective factors involved in that

* This point is discussed in a subsequent section of this paper.

TABLE I

Summary of the Data from 20 Cases Treated with Para-Aminobenzoic Acid (PABA)[1], Cairo, Egypt, 1944 and 1945

Case No.	Age, Years	Body Weight, Kg.	Duration of Illness When Treatment Was Begun, Days	Duration of Treatment, Days	Total Amount PABA Given, Grams	Maximum Blood Level PABA[2], mg. %	Lowest WBC/cu. mm.	Maximum N.P.N. mg. %[3]	Rash[4]	Maximum Titer[5]		*R. prowazeki* demonstrated##	Duration of Fever, Days	Duration of Secondary Fever, Days	Complications[6]	Final Score[7]
										Weil-Felix (OX19)	Complement Fixation (Epidemic antigen)					
1	32	54.0	1	8½	182	35	5,800	31	+	640	512	Yes	8¾	none	none	8¾
2	23	61.4	1¼	6½	168	5	7,500	30	?	640	1,024 NEP	Yes	6¾	none	none	6¾
3	18	63.2	1¾	13	294	27	3,250	45	+	10,240 NEP	80	N.A.	11¼	none	j	12¼
4	20	60.0	2	6	154	15	4,900	24	+	1,280	128	Yes	11½	none	none	11½
5	40	65.0	2¾	5	104	63	3,900	44	0	40	640	N.A.	5¾	none	none	5¾
6	34	48.6	3¾	11	224	40	5,250	46	++	10,240 NEP	320	N.A.*	12	none	j	13
7	18	51.8	4	7½	169	35	2,500*	43	++	10,240 NEP	320	N.A.	12½	3¼	none	15¾
8	20	56.0	4¼	4	94	.35	5,600	29	+	5,120 NEP	1,024 NEP	Yes	7¼	7	a, e	16¼
9	22	56.8	4¾	6	146	17	5,650	32	+	5,120 NEP	1,024 NEP	Yes	9¾	none	none	9¾
10	28	56.8	4¾	4	100	10	5,100	43	?	2,560	1,024 NEP	Yes	8¼	¼	none	8½
11	22	65.0	5	8	188	24	3,150	33	+	40	2,560 NEP	N.A.	10½	none	a	11½
12	30	53.2	5	11	195	43	4,200	31	++	5,120 NEP	1,024 NEP	Yes	14¾	none	none	14¾
13	23	47.8	5	5½	93	41	3,250	50	+++	negative	negative	N.A.	10½	none	a, b, j, m	33 (died)
14	35	58.2	5½	5	115	12	1,850**	32	+	5,120	1,024 NEP	Yes	8¾	none	none	8¾
15	33	61.4	5¾	11	235	24	5,000	40	+++	5,120	640	N.A.	16	¼	a, e, h	19¼
16	42	58.6	5¾	13	316	52	2,650*	45	++	5,120	640	N.A.	31¼	none	a, e, h, j	24
17	48	56.8	6	6½	148	13	3,350	39	++	80	1,024 NEP	Yes	16¼	none	a, b, d, h	20¼
18	35	50.0	6¼	7	164	33	3,450	46	+	160	1,024 NEP	Yes	12½	2½	j	16
19	27	51.4	6¼	12	238	52	3,450	35	+++	320	2,560 NEP	N.A.	19½	none	a	20½
20	20	59.5	6½	8	181	36	3,050	39	++	320	320	N.A.	10½	none	none	10½
Mean	28.5	56.8	4.4	7.9	175.4	30.6	4,100	37.8					12.8		1.6	14.3
S. D.	8.7	5.2	1.7	2.9	62.6	15.7	1,400	7.3					4.3***		3.0#	6.6

classification have been eliminated in the present analysis by computing a final score for each patient which is obtained by adding together the number of days of fever and the number of "complications." The latter term has been selected for convenience to represent those features of the clinical course of typhus which indicate the severity of the disease. Each complication is denoted in subsequent tables by a letter as follows:

a—delirium
b—stupor
c—coma
d—incontinence of urine and/or feces
e—pneumonitis
f—secondary bacterial infections (otitis media, or parotitis, or furunculosis)
g—gangrene
h—urinary retention
i—oliguria (less than 500 c.c. of urine in 24 hours)
j—blood nonprotein nitrogen (NPN) 45 mg. per 100 c.c. and above
k—blood nonprotein nitrogen 80 mg. per 100 c.c. and above
l—systolic blood pressure below 80 mm. Hg
m—pulse rate above 140 beats per minute, or gallop rhythm.

---

[1] Arranged according to the day of disease when treatment was begun.

[2] These values signify the highest level found throughout the course of treatment two hours following the preceding dose of PABA.

[3] When high blood levels of PABA were encountered, the total nonprotein nitrogen value has been corrected for the nonprotein nitrogen contributed by the presence of PABA. Values for the blood nonprotein nitrogen of 45 mg. per cent or more are interpreted as evidence for nitrogen retention or azotemia throughout this report.

[4] The rash is classified as follows: 0, none seen at any time; ?, questionably present; +, light; ++, moderate; +++, profuse.

[5] NEP indicates that the end point was not reached, the value being the highest dilution tested.

[6] These symbols are interpreted as follows: (*a*) delirium; (*b*) stupor; (*c*) coma; (*d*) incontinence of urine and/or feces; (*e*) pneumonitis; (*f*) secondary bacterial infections (otitis media, parotitis or furunculosis); (*g*) gangrene; (*h*) urinary retention; (*i*) oliguria (less than 500 c.c. urine in 24 hours); (*j*) blood nonprotein nitrogen 45 mg. per cent and above; (*k*) blood nonprotein nitrogen 80 mg. per cent and above; (*l*) systolic blood pressure below 80 mm. Hg; (*m*) pulse rate above 140 beats per minute, or gallop rhythm.

[7] For calculation of final score see text.

* Further treatment of this patient was discontinued because of the low white blood cell count.

** The low white blood cell count developed three days after cessation of treatment.

*** Mean and standard deviation refer to total fever (primary plus secondary), with maximum set at 20 and fatal case counted as 20. See text for explanation.

Mean and standard deviation calculated on basis of 13 complications for fatal cases. See text for explanation.

"*R. prowazeki* demonstrated" means that the following criteria were satisfied: (*a*) Demonstration of morphologically typical intracellular coccobacillary forms in bacteria-free yolk sac suspensions and/or cotton rat peritoneal or mediastinal exudates, following inoculation with passage material derived from patient's blood, or from normal lice which were fed on the patient during the febrile period; (*b*) reciprocal cross immunity with Breinl strain of *R. prowazeki* as tested by fatal challenge doses in cotton rats; (*c*) development of specific antibodies in sera of cotton rats or guinea pigs following inoculation of material in question. The letters N.A. mean that no attempt was made to isolate rickettsiae.

TABLE II

Summary of the Data from 19 Alternate Control Cases,[1] Cairo, Egypt, 1944 and 1945

Case No.	Age	Body Weight, Kg.	Duration of Illness When Admitted, Days	Lowest WBC/cu. mm.	Maximum N.P.N., mg. %	Rash[4]	Highest Titer[5]		*R. prowazeki* Demonstrated##	Duration of Continuous Fever, Days	Complications[6]	Final Score[7]
							Weil-Felix (OX19)	Complement Fixation (Epidemic Antigen)				
1	21	48.2	¾	5,950	35	+++	40	1,024 NEP	Yes	24¼	a, b, d, f	24
2	30	54.1	2¼	3,250	45	+	2,560	1,280	N.A.	14¾	a, b, d, e, h, j, m	21¾
3	30	52.7	2½	4,300	109	+	80	640	Yes	9¼	a, b, c, d, i, j, k, l, m	33 (died)
4	21	57.0	2¾	9,650	38	+++	5,120 NEP	1,280	Yes	16¼	a, b, d, h	20¼
5	18	54.1	2¾	4,450	40	++	40	640	N.A.	15¼	e, m	17¼
6	18	54.6	3¾	5,900	88	+++	10,240 NEP	640	N.A.	12¼	a, b, c, d, e, h, j, k, l, m	33 (died)
7	26	60.0	3¾	3,400	200	+++	2,560	negative	Yes	8¾	a, b, c, d, h, i, j, k, m	33 (died)
8	22	49.0	4¼	14,650	29	+++	1,280	640	Yes	28½	a, b, d, f	24
9	46	51.8	4¼	6,200	110	+++	640	5,120	Yes	17½	a, b, c, d, e, j, k, l, m	33 (died)
10	25	67.3	4½	1,900	50	+++	80	2,560 NEP	Yes	26¾	a, b, d, h, j, m	26
11	25	49.1	4¾	4,900	48	+++	2,560	1,280	N.A.	19½	a, d, j, h, m	24½
12	25	55.0	5	4,900	75	+	5,120 NEP	640	Yes	18½	a, b, c, d, f, g, h, j	26½
13	38	57.3	5¼	4,100	47	+++	10,240 NEP	160	N.A.	12¾	a, e, j	15¾
14	43	58.6	5¼	2,550	75	++	2,560	1,280	Yes	12½	a, b, c, e, i, j	33 (died)
15	41	50.5	5¾	4,150	63	0	40	160	N.A.	15¼	a, b, j, m	33 (died)
16	23	46.4	6¼	3,300	33	++	10,240 NEP	640	N.A.	18	a, b, d, m	22
17	24	46.0	6¼	4,400	40	++	5,120 NEP	640	Yes	15½	a, b, e, m	19½
18	35	59.1	6¾	7,600	42	?	2,560	320	N.A.	11½	none	11½
19	20	55.5	7¼	3,900	41	+	320	2,560 NEP	N.A.	17¾	m	18¾
Mean	27.9	54.0	4.4	5,200	63.6					17.9***	6.8#	24.7
S. D.	8.6	5.3	1.7	2,900	41.1					2.7***	4.7#	6.8

[1] For explanation of data in this table see footnotes for table 1.

The febrile period in uncomplicated typhus rarely lasts longer than 20 days. Longer periods of fever are caused by various complications, particularly secondary infections. Since complications contribute independently to the final score, the maximum duration of fever is set arbitrarily at 20 days. In computing the score for a fatal case, it is assumed that such a patient had the maximum duration of fever and the maximum number of complications, the score being 33. Theoretically, a surviving patient could have had a score of 33, but actually this was not found.

Presentation of Data. Tables 1 and 2 contain the data for the 39 patients in the alternate treated and control groups. The patients are arranged according to the duration of illness at the time they were admitted to the study groups. Various data, including age, duration of fever, lowest white blood cell count, highest blood nonprotein nitrogen, maximum titer in serologic tests, incidence of complications and final score, are indicated for the control cases. For the treated cases the same data are reported, as well as the duration of PABA therapy, the highest concentration of PABA in the blood, and the total amount of drug given.

Figure 1 shows the temperature curves of the two groups. The points on the curves represent the means of the rectal temperature readings for each day of illness for all the cases in each group. The number of observations contributing to the mean is six times the number of patients, since each

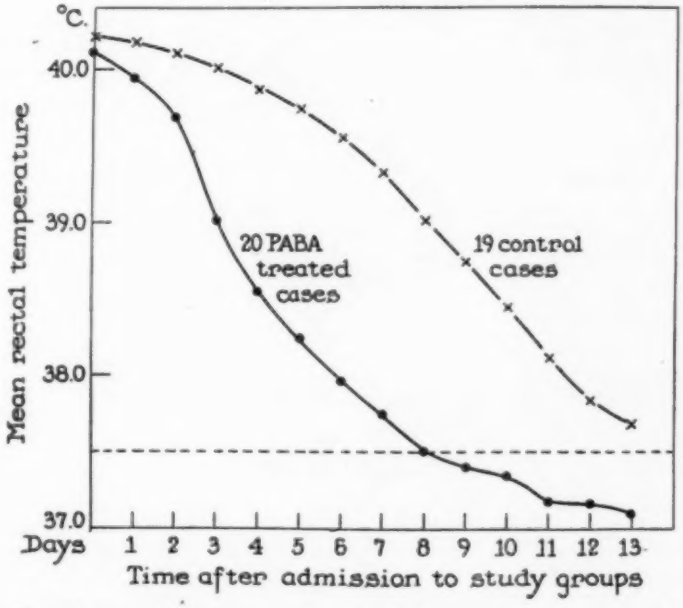


FIG. 1. Comparison of temperatures of 20 PABA-treated patients and 19 alternate control patients, Cairo, Egypt, 1944 and 1945. Mean daily rectal temperatures are plotted for each group, zero day being the day of admission of each patient to the study (the mean duration of illness at the time of admission for both groups was 4.4 days). The temperatures of fatal cases are included up to the last reading before death occurred.

patient had his temperature taken six times daily. The readings observed on the day of admission to the study groups are plotted at the zero point, and the readings on the successive days are indicated for the following 13 days. The fatal cases are included up to the last reading before death. The mean value in the treated group fell below 37.5° C. on the eighth day after treatment was begun. The mean value for the control cases had not fallen to that point by the thirteenth day.

Analysis of Data

The 19 patients in the control group had mean values as follows: age, 27.9 years; duration of illness when admitted to the group, 4.4 days; duration of fever, 17.9 days; number of complications, 6.8; final score, 24.7. Six patients in the control group died.

The 20 patients in the PABA-treated group had mean values as follows: age, 28.5 years; duration of illness when treatment began, 4.4 days; duration of fever (primary plus secondary), 12.8 days; number of complications, 1.6; final score, 14.3. One patient in the treated group died.

The scatter of the values about the means for both groups is expressed as the standard deviation (S. D.) shown in tables 1, 2, and 3.

These figures indicate that the control and treated groups were nearly identical as regards mean age and mean duration of illness when admitted, but that there were large differences in duration of fever and number of complications between the two groups. The statistical significance of the differences has been computed using "Student's" *t* test. The results are shown in table 3. The difference in mean duration of fever in two groups

Table III

Values of *t* for the Differences between Control and PABA-Treated Groups, Cairo, Egypt, 1944 and 1945, as Regards Duration of Fever, Number of Complications and Final Score

	Means and Standard Deviations		Difference between the Means	Standard Deviations (both groups combined)	"t"*	p
	Control	Treated				
Duration of fever (days)	17.9, 2.7	12.8, 4.3	5.1	4.4	3.6	0.001
Number of complications	6.8, 4.7	1.6, 3.0	5.2	4.7	3.5	<0.01
Final score	24.7, 6.8	14.3, 6.6	10.4	8.4	3.9	<0.001

* "t" calculated in manner described by Mainland "Treatment of Clinical and Laboratory Data," Oliver and Boyd, London, 1938, p. 157.

of this size would be expected to occur by chance only once in approximately 1,000 trials; the difference in number of complications once in more than 100 times; and the difference in score once in more than 1,000 trials. It is highly unlikely, therefore, that the differences were due to chance.

It might be argued that the differences are due to the inclusion of fatal cases with arbitrarily assigned maximum scores. To examine this point, a

comparison of the duration of fevers in the two groups was made in which only surviving patients were considered. This showed 16.9 days for controls and 12.4 days for PABA-treated cases. For this difference t is 2.97 and p is less than 0.01. In a similar manner the incidence of complications has been compared in the two groups, counting for the fatal cases only those complications which were noted in each instance, rather than the maximum number. The mean values are 5.2 for controls and 1.1 for PABA treated cases; t for this difference is 4.20 and p is less than 0.001. The arbitrary standards used in computing the scores for the fatal cases do not, therefore, give rise to the differences between the two groups. In the following paragraphs other factors are considered which might have contributed to the difference between the control and the PABA-treated groups.

Age. The mortality from typhus increases with age. An unequal age distribution between the groups might produce differences in duration of fever, number of complications, and score. To examine this factor more closely, the control and treated patients have been arranged according to age in table 4. It is obvious from inspection of this table that the age distribution is essentially identical in the two groups. The differences in score cannot be attributed to age difference.

TABLE IV

Comparison of Ages of Control and PABA-Treated Patients, Cairo, Egypt, 1944 and 1945

	Ages	
	Control	Treated
	18, 18, 20, 21 21, 22, 23, 24 25, 25, 25, 26	18, 18, 20, 20 20, 22, 22, 23 23, 27, 28
	30, 30, 35, 38	30, 32, 33, 34 35, 35
	41, 43, 46	40, 42, 48
Mean	27.9	28.5
S. D.	8.6	8.7

Duration of Illness at Time of Admission to the Study Groups. The data in tables 1 and 2 show that the mean duration of illness at the time of admission was identical for the PABA-treated group and the control group. Thus, there is no evidence that the differences in duration of fever and number of complications could be attributed to this factor. However, it is of interest to determine whether, within each group, there was any relation between the duration of illness at the time of admission and the final score.

In figure 2 the final scores of control and PABA-treated cases are plotted against duration of illness at the time of admission. In the control group the points are widely scattered. Calculation shows that the coefficient of correlation, r, is -0.24. Thus, in the control group there is no evidence that the duration of illness at the time of admission (up to the end of the

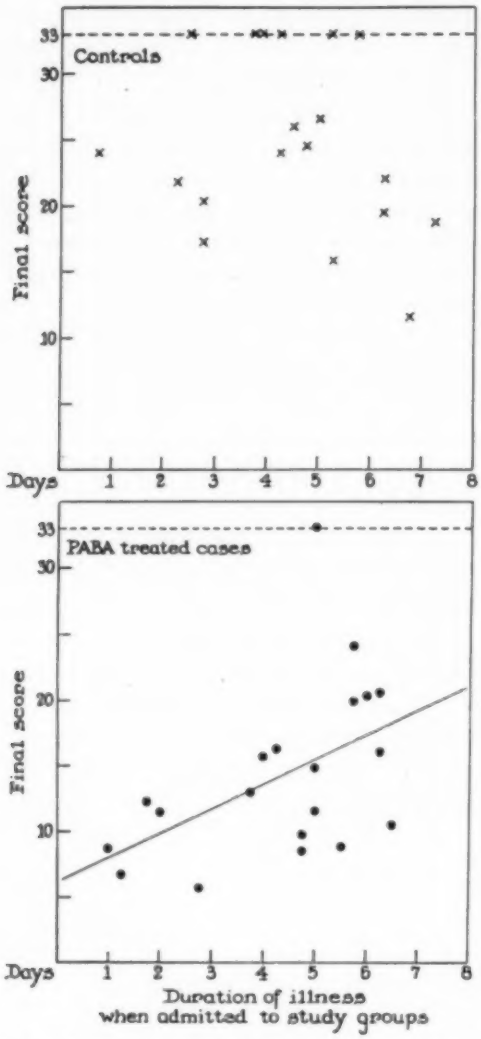


FIG. 2. Comparison of final score and duration of illness when admitted to the study groups. Control patients charted above, PABA-treated patients below. Fatal cases given score of 33.

seventh day) has any relation to the severity as judged by the final score (duration of fever plus number of complications).

On the contrary, however, the points in figure 2 for the PABA-treated cases suggest a definite relationship between the duration of illness when treatment was begun and the final score. The coefficient of correlation, r, is found to be $+ 0.481$. For this value of r, p lies between 0.05 and 0.02. It may be stated, therefore, that the observed relationship would not be expected to occur by chance. It should be noted in considering this correlation that the patients who were admitted near the end of the first week of illness already had accumulated a higher initial score and that the possibility of a

difference in final score occurring between the control and the treated patients was thereby reduced. By extrapolating the trend of the relationship it appears that the final score in the treated group would attain a value equal to the mean final score of the untreated patients between the tenth and eleventh days. Controlled data on this point are not available, but it is likely that a very large group of patients would be required to evaluate an effect of PABA if treatment were first begun more than eight days after the onset of illness.

Comparison of Cases Treated in 1944 and 1945. Since the data in this analysis were obtained in two different seasons, it is important to determine whether there were differences in the severity of the epidemics in the two years, and whether the study groups in the two seasons have comparable values for final scores.

The figures for the entire population of male Egyptian typhus patients, ages 18 to 48, admitted to the general wards of the Cairo Fever Hospital in May and June 1944 (the period covered by the 1944 alternate series) were as follows: 156 cases, 46 deaths (29.5 per cent mortality). For the period covered by the 1945 alternate series (April and May) the figures were: 215 cases, 64 deaths (29.8 per cent mortality). The age distributions were nearly the same in the two periods. It appears that the populations from which the study cases were drawn in 1944 and 1945 were essentially identical as regards mortality.

In the study groups themselves, the mean values for duration of fever and incidence of complications observed in 1944 have been compared with the mean values observed in 1945. No significant differences were present between the control groups in the two years; there is thus no evidence that they were not drawn from the same population.

However, for the PABA-treated group, the mean final score in 1945 was greater than the mean score in 1944. Although the difference in score is not great enough to be statistically significant, it is interesting to note that the mean duration of illness at the time of admission for the 1945 patients was slightly greater than that of the 1944 patients. On the basis of the correlation described in a preceding section the 1945 patients would be expected to have a slightly higher score.

Mortality. Six of 19 control patients died; one of 20 treated patients died. A difference of this magnitude would be expected to occur by chance only once in 26 samples of this size.[17]

The pathologic findings in the fatal PABA-treated cases are discussed in the appendix.

Comparison of White Blood Cell Counts. It was noted previously[12] that PABA tended to depress the white blood cell count. The data are adequate to permit a rough comparison of the difference in lowest counts in the treated and control groups (tables 1 and 2). The mean of the lowest counts for the 19 alternate controls was 5,200. The mean for the alternate

PABA-treated patients was 4,100. This difference is not statistically significant ($t = 1.49$; p lies between 0.1 and 0.2). The differential counts recorded at, or close to, the time of the lowest white blood cell count for each patient have been used to calculate the mean values for the differentials, which are shown in table 5. The depression of total white blood cell count in the

TABLE V

Mean Values for the Differential Counts* of Alternate Treated and Control Groups at, or Close to, the Time of Lowest Recorded White Blood Cell Count, Cairo, Egypt, 1944 and 1945

	Mean of Lowest White Blood Cell Counts	Mean Values of Differential Counts Taken at, or Close to, the Time of Lowest White Blood Cell Count†					
		P	L	M	E	B	Uncl.
19 control patients	5,200	69.9	25.3	1.2	0.6	0.8	2.3
20 PABA-treated patients	4,100	55.1	38.4	1.5	1.2	0.4	3.4
Difference between control and treated	1,100	14.8	13.1	0.3	0.6	0.4	1.1
Standard deviation of both groups combined	2,300	13.6	12.8	1 5	1.4	0.9	
"t" = p =	1.49 <0.2 >0.1	3.4 <0.01	3.2 <0.01	0.6 <0.6 >0.5	1.3 0.2	1.4 <0.2 >0.1	

* The figures are based on numbers of cells in each 100 counted.
† P = polymorphonuclear cells; L = lymphocytes; M = monocytes; E = eosinophiles; B = basophiles; Uncl. = unclassified.

PABA-treated cases was accompanied by a statistically significant reduction in the percentage of polymorphonuclear cells and a similar increase in the percentage of lymphocytes. The differences in percentages of monocytes, eosinophiles, and basophiles were not statistically significant.

Summary of the Statistical Analysis of the Data. Thirty-nine male Egyptian patients, aged 18 to 48 years, suffering from proved typhus fever, were studied in the Typhus Commission Ward in the Cairo Fever Hospital, in 1944 and 1945, at the peaks of the epidemics in those seasons. The patients were in their first week of illness when admitted to the study groups. Alternate cases were treated with large amounts of PABA; these patients had shorter fever, fewer complications, and a lower mortality rate than the untreated controls. The differences were found to be statistically significant. Factors which might have been of importance in producing the differences were considered. These were age distribution, duration of illness when admitted to the study groups, and variation in the severity of the epidemics in 1944 and 1945. No evidence was found that these factors contributed to the differences between PABA-treated and control groups.

Within the PABA-treated group itself there was a significant correlation between the duration of illness when therapy was begun and the final score (composed of days of fever plus the number of complications).

PART II

Use of PABA in the Typhus Fever Epidemic in the Dachau Concentration Camp in Germany, May 1945

In the preceding sections the controlled clinical trial of PABA in typhus fever has been presented in detail. We were convinced by this experience that the drug definitely lessened the severity of the illness when treatment was begun early in the disease and when sufficiently large amounts were given to produce an adequate concentration of the drug in the blood during the entire period of therapy.

In May 1945 an opportunity arose to apply the experience with PABA to the outbreak of typhus fever in the Dachau Concentration Camp in Germany. The United States Seventh Army liberated Dachau on April 29, 1945. The wretchedness and the horrible conditions encountered among the forty thousand inmates of this camp defy description. Starvation, tuberculosis, and typhus fever were claiming more than 100 lives daily at the end of April. The medical staffs of the United States Forces which took over the hospitalization at Dachau made every effort to give the inmates a maximum of help. The attempt was made to vaccinate all of the people in the camp with Cox-type vaccine and to apply DDT anti-louse powder to the clothes and sleeping quarters of everyone in the quarantine zone. At least two-thirds of the inmates received typhus vaccine and nearly all had their clothes dusted. In addition, arrangements were made to treat typhus patients with PABA. It should be emphasized strongly that the use of PABA at Dachau was not undertaken as an experimental study. Despite many difficulties, therapeutic amounts of PABA were administered to 60 male patients who had typhus fever.[18] The data are summarized in table 6.

Selection of Patients for Treatment. The attempt was made to treat those patients whose condition suggested that they would run a severe course of typhus fever. The circumstances in the camp made it exceedingly difficult to begin treatment early in the disease. For the majority of patients treatment was not begun until the fifth to the seventh day. The age of the patients varied from 17 to 71 years, with a mean age of 32.6 years. Fifteen of the patients gave their nationality as French, 14 as Hungarian, eight as German, six as Russian, five as Polish, and four as Czechoslovak. Three patients came from Austria, two from the Netherlands, one from Greece, one from Norway, and one from Alsace Lorraine.

Complicating Conditions at the Time Treatment Was Begun. Severe malnutrition was noted in 13 patients on their admission for treatment. Other conditions such as edema, diarrhea, hematuria, and azotemia were observed. Pulmonary tuberculosis was known to be present in at least three of the patients.

Plan of Treatment. Chemically pure PABA was given by mouth in powder form mixed with a 5 per cent solution of sodium bicarbonate. At

TABLE VI

Summary of the Data from 60 Cases of Louse-Borne Typhus Treated with Para-Aminobenzoic Acid at Dachau Concentration Camp, Dachau, Germany May-June 1945[1]

Case No.	Age, Years	Nationality[8]	Duration of Illness when Treatment Was Begun, Days	Duration of Treatment, Days	Total Amount Para-Aminobenzoic Acid Given, Gm.	Maximum Blood Level of Para-Aminobenzoic Acid,[2] Mg. %	Lowest W.B.C. per Cu. Mm.	Maximum N.P.N.[3] Mg. %	Rash[4]	Duration of Fever, Days[7]	Maximum Titer[5]		Associated Conditions on Admission[6]	Complicating Conditions Occurring during Hospitalization[6]	Severity of Clinical Course	Typhus Vaccine, Number of Injections[9]	Remarks
											Weil-Felix	Complement Fixation					
1	20	Hu.	3	10	191	41	5050	44	+	9	10,240 NEP	40	0	0	mild	2	Strain isolated.
2	29	Cz.	3	8	146	17	2300	41	++	12	5,120	160	0	0	mild	2	
3	37	Pl.	3	9	165	32	3200	54	+	12+3	1,280	80	j, n	f	mild	2*	
4	24	Cz.	3	7	186	41	5200	75	+	7	2,560	160	j	0	mild	2	70 grams of PABA I.V.
5	22	Ru.	4	9	165	61	2300	35	+	15+6	320	320	p, x	0	mild	2	Penicillin for infection.
6	36	Gr.	4	8	140	56	3550	34	++	11	5,120	160	0	0	mild	2*	
7	37	Gr.	4	7.5	139	55	4450	—	?	8	1,280	neg.	p	0	mild	—	
8	47	Hu.	4	7	131	38	4950	60	0	11+2	5,120	320	j	0	moderate	2*	PABA discontinued when febrile, due to shortage of drug.
9	36	Gr.	4	11.5	222	36	3950	61	+	16	10,240 NEP	320	j	e	moderate	1	
10	19	Fr.	4	8	178	31	4100	60	+	9	1,280	160	j	0	moderate	2	Strain isolated.
11	27	Ru.	4	7.5	223	24	4900	43	0	13	640	80	0	0	mild	2*	
12	22	Hu.	5	10	184	32	4800	42	++	13	10,240 NEP	640	0	0	moderate	2	Strain isolated.
13	26	Hu.	5	5	75	67	2900	54	+	9	10,240 NEP	320	j, p	0	mild	2	
14	25	Hu.	5	5	97	40	5350	44	0	7	10,240	640	0	0	mild	2*	Strain isolated. PABA discontinued because of vomiting when patient was afebrile.
15	22	Gr.	5	8	133	48	3600	50	0	23	2,560	80					
16	23	Fr.	5	7	129	45	3000	50	++	12	10,240 NEP	40	j, p, q	0	mild	2	Probable enteric fever following typhus.
17	25	Nr.	5	7	136	31	2150	34	+	10	320	320	j	0	mild	2*	
18	24	Hu.	5	8	141	57	3150	55	++	11	10,240 NEP	320	p	0	mild	0	
19	42	Fr.	5	6	109	38	3700	36	++	10+1	5,120	320	0	j, n	moderate	2*	
20	37	Fr.	5	9.5	174	38	3250	41	?	11+4	1,280	160	p	0	mild	2	
21	32	Hu.	5	8	115	24	5500	35	+	10+4	10,240 NEP	160	r	0	moderate	2*	
22	33	Hu.	5	4	99	10	7750	53	+	8	2,560	80	0	0	mild	0	Strain isolated.
23	50	Hu.	6	9	158	36	4300	43	+	14+8	10,240 NEP	160	j, p	0	mild	2*	Strain isolated.
24	18	Gk.	6	8	135	61	2850	38	0	11+1	10,240 NEP	160	f	0	mild	1	Sulfadiazine for cellulitis associated with furunculosis in convalescence.
25	36	Pl.	6	2	48	93+	4500	150	0	10	640	neg.	0	0	mild	—	
26	34	Gr.	6	10	171	66	3550	37	+	14	10,240 NEP	1,280	k, n, s	y	fatal	—	Died on 10th day. Autopsy: see appendix.
27	27	Gr.	6	3	47	36	1300	36	+	15+4	10,240 NEP	320	0	r, z	mild	2*	
28	52	Gr.	6	7	98	54	3900	38	++	12+3	1,280	640	t, z	e, r	severe	2*	Chronic alcoholism. I.V. plasma.
													0	z	mild	2*	
29	41	Fr.	6	11	186	56	2450	41	+++	14+7	160	132	r	r	moderate	1	
30	32	Fr.	6	3	56	41	1300	38	?	9+13	10,240 NEP	160	p	e	mild	2	13 days secondary fever associated with chest signs of pneumonitis. X-ray consistent with atypical pneumonitis.

TABLE VI—*Continued*

Case No.	Age, Years	Nationality[5]	Duration of Illness when Treatment Was Begun, Days	Duration of Treatment, Days	Total Amount Para-Aminobenzoic Acid Given, Gm.	Maximum Blood Level of Para-Aminobenzoic Acid,[2] Mg. %	Lowest W.B.C. per Cu. Mm.	Maximum N.P.N.,[3] Mg. %	Rash[4]	Duration of Fever, Days[7]	Maximum Titer[6]		Associated Conditions on Admission[6]	Complicating Conditions Occurring during Hospitalization[6]	Severity of Clinical Course	Typhus Vaccine, Number of Injections[8]	Remarks
											Weil-Felix	Complement Fixation					
31	27	Fr.	6	8	127	45	2250	41	+	11	10,240 NEP	160	u	0	mild	2*	Artificial pneumothorax—right lung.
32	26	Fr.	6	8	158	28	5450	40	+	13	10,240 NEP	80	p	0	mild	2*	
33	30	Pl.	7	5	96	30	3750	52	++	12	640	640	j	0	mild	2	
34	22	Pl.	7	7	113	55	3100	50	++	11+1	1,280	320	j	0	mild	—	Strain isolated.
35	24	Hu.	7	6.5	124	40	3900	41	?	12	5,120	160	0	0	mild	2*	Strain isolated.
36	20	Ru	7	8	152	41	5050	35	+	15	10,240 NEP	320	0	0	moderate	2	
37	54	Au.	7	5	82	41	3150	54	+++	12	320	40	j	0	fatal	2	Sudden death, 12th day. Autopsy: see appendix.
38	26	Du.	7	6	115	43	4050	38	++	10	1,280	640	0	0	mild	2*	
39	43	Fr.	7	10	211	32	3350	36	+++	17+2	5,120	320	0	e	severe	2	
40	25	Fr.	7	11	221	35	3850	42	+++	17	10,240 NEP	640	n	e	severe	2	
41	24	Fr.	7	7	120	44	8100	50	++	13	1,280	320	0	j	severe	2*	
42	41	Fr.	7	11	189	41	2150	53	++	14	2,560	640	j	0	moderate	2	
43	58	Au.	7	7	146	18	3750	38	+	14	10,240 NEP	160	0	0	moderate	0	
44	21	Cz.	7	11	340	69	5150	90	+	14	10,240 NEP	640	n	T.P., k	mild	2	205 gm. PABA I. V. over four days.
45	17	Ru.	7	3	40	63	3750	40	0	13+1	10,240 NEP	640	0	0	mild	2	40 gm. PABA I. V.
46	48	Au.	8	8	143	55	5550	—	+++	13+1	320	640	0	0	mild	0	
47	21	Hu.	8	7	128	35	5400	42	+	12+1	10,240 NEP	320	0	0	mild	2	
48	57	Al.	8	9	149	34	1650	34	++	16	320	640	p, r, v	z	moderate	2*	Plasma I. V.
49	30	Du.	8	7	145	35	2700	39	++	14	2,560	160	0	e	moderate	2*	
50	41	Fr.	8	7	132	35	4200	40	+	14	160	80	p	0	mild	2	
51	32	Hu.	9	8	154	52	3000	37	++	15	1,280	160	p	0	moderate	2*	
52	20	Fr.	10	7	118	67	3850	60	++	16	10,240 NEP	320	j, n	e	moderate	2*	
53	32	Hu.	11	12	222	65	4050	36	+++	31	320	640	0	d, e	severe	—	Strain isolated. Refused PABA on 3 occasions.
54	71	Ru.	11	10	228	19	3800	44	++	17+1	10,240 NEP	1,280	n, u	0	mild	0	
55	46	Gr.	16	7	97	54	5350	109	+++	21+14	10,240 NEP	2,560	k, n, p	f, k, r	severe	2*	
56	35	Hu.	3	13	348	45	3600	35	0	27+	2,560	160	u	f	moderate	2	TBC right lung. Positive sputum.
57	31	Cz.	5	11	271	30	2600	41	++	19+	640	160	n	e, z	severe	0	75 grams PABA I. V.
58	35	Fr.	?	2	41	40	5550	46	++	?	neg.	neg.	j, u	0	fatal	2*	Sudden death, 4th hospital day. Autopsy: see appendix.
59	22	Ru.	?6	8	189	12	4150	47	+++	?13	1,280	320	f, n	f, j	severe	2	
60	39	Pl.	?6	8	156	45	2600	40	+	?12+1	2,560	320	p	0	mild	2*	

Footnotes 1, 2, 3, 4, and 5 as in table 1.

[6] These symbols are interpreted as follows: a, delirium; b, stupor; c, coma; d, incontinence of urine and/or feces; e, pneumonitis; f, secondary bacterial infections (otitis media, parotitis or furunculosis); g, gangrene; h, urinary retention; i, oliguria (less than 500 c.c. urine in 24 hours); j, blood nonprotein nitrogen 45 mg. per cent and above; k, blood nonprotein nitrogen 80 mg. per cent and above; l, systolic blood pressure below 80 mm. Hg; m, pulse rate above 140 beats per minute, or gallop rhythm; n, hematuria; p, malnutrition; q, conjunctivitis; r, diarrhea; s, epilepsy; t, cirrhosis, ascites; u, pulmonary TBC; v, hypoproteinemia; w, scabies; x, gun shot wound, left hand; y, convulsions; z, edema; T.P., thrombophlebitis.

[7] When a second period of fever occurred, it is indicated by the second figure in the column.

[5] Key to nationality. Al = Alsatian, Au = Austrian, Cz = Czechoslovakian, Du = Dutch, Fr = French, Gk = Greek, Gr = German, Hu = Hungarian, Pl = Polish, and Ru = Russian.

[8] 0 = no vaccine, — = doubtful, 1 = 1 c.c., 2 = 2 c.c., 2* = probably more than 2 c.c. of Cox-type vaccine administered by the U. S. Army. These data were obtained only from questioning each patient. See text for discussion of typhus immunization at Dachau.

Note: The isolation of rickettsial strains from certain patients in this service was performed by feeding a colony of uninfected stock lice on the leg for 7 to 10 days, or by inoculation of ground blood clot into guinea pigs.

least 20 c.c. of bicarbonate solution was given for each gram of drug, but the amount of bicarbonate was increased from time to time depending upon the determination of the pH of freshly voided urine specimens. The majority of patients received the drug every two hours, day and night. At some time during their course of therapy a few patients received the drug at intervals of four hours. The initial dose varied from 4 to 6 gm. and subsequent doses ranged from 1 to 3 gm. depending upon the blood concentration, which was determined at least once every 24 hours in all cases and at intervals of four hours in some. The white blood cells were counted at least once every two days for all patients under treatment. When low counts were found, differential counts were performed as often as possible. Treatment with PABA was continued until the temperature had reached normal levels for 24 hours or longer. A temporary shortage of the drug occurred at one time, interrupting treatment in a few patients who were still febrile. Four patients received varying amounts of the sodium salt of PABA by continuous intravenous infusion. The salt was dissolved in physiological saline solution in concentrations of from 1 to 5 per cent. The longest period of intravenous administration in any patient was four days. The thrombophlebitis which occurred in two patients during this form of therapy probably was attributable to inadequate buffering or improper sterilization of the solutions.

Supportive Therapy. Plasma infusions, parenteral saline injections, and specific treatment of secondary bacterial infections with penicillin or sulfonamide drugs were given as conditions required.

Complications Arising during the Course of Treatment. After five days of therapy one patient experienced nausea and vomiting; since he had become afebrile PABA was discontinued. Another patient refused further therapy after seven days of treatment. In the remaining 58 cases no serious difficulties were encountered in the oral administration of the drug.

A white blood cell count of less than 3,000 per cubic millimeter was observed in nine patients who were still febrile and receiving PABA; their treatment was continued for one to four days after the low count was noted. Six patients were first found to have counts below 3,000 after PABA therapy had been stopped. The lowest value among the Dachau patients was 1,600, which was found 24 hours after cessation of treatment. The differential showed 62 per cent polymorphonuclear leukocytes at that time.

Under observation none of the patients with leukopenia showed any evidence of secondary infection commonly associated with agranulocytosis. One patient was still febrile but not receiving PABA on the nineteenth day of disease, when it was necessary to transfer him to another hospital, and the ultimate outcome of his illness is not known. The remaining 14 patients with low white counts were all discharged as cured of typhus.

In 24 patients the blood nonprotein nitrogen rose above 45 mg. per 100 c.c. during the course of treatment with PABA, and in two patients micro-

scopic hematuria developed. These findings have been observed frequently in patients with louse-borne typhus who are not receiving PABA.

Physical signs or roentgenographic evidence of pneumonitis were observed in nine of the 60 patients.

A secondary rise in oral temperature above 37.3° C. occurred in 19 patients after their temperatures had been normal for at least 24 hours. In seven of the 19 patients this secondary febrile period could be accounted for by such conditions as otitis media, wound infection, abscesses, continuing diarrhea, or pneumonitis. In the remaining 12 patients the cause of fever was obscure. Although the possibility of active pulmonary tuberculosis was not ruled out, the oral temperature was rarely more than 37.8° C. and the fever lasted only a short time. It was associated with practically no symptoms. In some of these cases the secondary fever may have been caused by a mild recrudescence of typhus which occurred because PABA was withdrawn prematurely.

The Severity of the Clinical Course of the Typhus Patients Treated with PABA at Dachau. It was our impression that the patients at Dachau derived benefit from treatment with PABA. The clinical courses of the 60 patients were classified as follows: 34 mild, 15 moderate, and eight severe. Three patients died. The 60 patients had shorter fever, fewer complications due to typhus, and fewer deaths than would be expected to occur in a group of that size suffering from classical louse-borne typhus fever. The clinical courses of the patients whose treatment was begun early in their illness were milder than those of the patients whose treatment was begun late.

More specific comments on the benefit derived by the patients at Dachau from treatment with PABA are not justified. The use of the drug at Dachau was not intended as an experimental study; there were no alternate control patients. Furthermore, the attempt was made to vaccinate everyone in the camp in the first two weeks of May 1945. Individual vaccination records were not kept. A *typhoid* immunization program was carried out simultaneously. Many of the patients admitted for treatment with PABA did not know accurately, if at all, how much *typhus* vaccine they had received. Probably most of the 60 patients listed in table 6 received one or more doses of this vaccine. In almost all instances, however, the patients were in the incubation period of typhus at the time they were vaccinated. There is only meager evidence relating to the effect of administering Cox-type vaccine in the incubation period of typhus.[19] It is possible that the vaccination program at Dachau reduced the severity of the cases in the entire camp. The precise figures are not known, but the overall mortality from typhus fever at Dachau was approximately 10 per cent for the cases under the care of the United States Army Medical Officers in May and June 1945.

Toxicity of PABA. In spite of their relatively poor physical condition, the 60 typhus patients who were treated at Dachau tolerated PABA remarkably well. It was not necessary to interrupt therapy during the febrile period

because of nausea and vomiting or leukopenia. Some patients received more than 250 grams of the drug in the course of several days of treatment, and concentrations in the blood, measured two hours after the preceding dose of PABA, were higher than 60 mg. per 100 c.c. in several instances. There were no clinical findings in this group of patients which were interpreted as evidence of toxic reactions to PABA, other than the depression of the white blood cell count. In one of the three fatal cases the kidneys showed microscopic evidence of a nephrosis. The significance of this finding is discussed in the next section.

Clinical Summary of the Fatal Cases

The gross and microscopic findings in the fatal cases are described in the Appendix. Three of the four patients presented the clinical features of classical louse-borne typhus (case 13, table 1, and cases 37 and 58 in table 6); they were febrile at the time of death. Throughout hospitalization they had tolerated PABA therapy well. Two of them (no. 37 and no. 58) were considered to be almost convalescent. They died suddenly in bed with no warning. Patient no. 13 became progressively worse during treatment, with increasing rash, delirium, and rising blood nonprotein nitrogen. However, he continued to take the drug until the time of death, the immediate cause of which appeared to be respiratory failure.

The fourth patient who died (no. 25, table 6) showed no rash. In other respects his clinical illness was consistent with typhus fever as complicated by familial epilepsy. He had suffered periodic convulsions from the age of 10. After the administration of 38 gm. of PABA over a period of 36 hours, he experienced several convulsive seizures. The blood nonprotein nitrogen was first determined at this time and found to be 140 mg. per 100 c.c. At the same time the blood concentration of PABA was above 90 mg. per 100 c.c. Therapy was discontinued at once. Nine hours after the first convulsive seizure the patient lapsed into coma; he died 11 hours later. In our opinion the high blood level of PABA obtained in this case after 36 hours of therapy and the greatly elevated blood nonprotein nitrogen were due to preexisting renal disease. It seems improbable that the severe kidney lesions found at autopsy could have been the result of PABA therapy of such short duration. This case illustrates the importance of a knowledge of renal function in patients receiving PABA and the necessity for frequent determination of the concentration of the drug in the blood. Further consideration of this aspect of treatment is dealt with later in this report.

Miscellaneous Patients Treated with PABA

In addition to the 20 patients whose cases are presented in the first report [12] and the 70 additional patients discussed in the preceding sections of this paper (see footnote on page 2 for tabulation of cases), we have treated

a miscellaneous group of five typhus patients. In this group there were three Egyptians and two Americans. In four patients the illness was mild, and possibly PABA therapy may have been of some benefit. No definite statement can be made, however, since the time of onset of illness was not known in two instances, and in the other two cases there had been repeated vaccinations against typhus before the onset of illness.

The fifth typhus patient in this miscellaneous group was started on treatment on the third day of illness. He was highly uncoöperative and refused therapy after less than two days of treatment. For that reason he was transferred to the general wards of the Cairo Fever Hospital where he developed the characteristic clinical course of typhus fever and died on the tenth day.

A few patients with diseases other than typhus were also given PABA: one patient with malaria, one with typhoid fever, and two with fever of unknown origin. PABA had no apparent effect on the course of malaria or typhoid. There were no untoward reactions observed in this group.

PART III

Points of Importance in the Use of PABA in Human Rickettsial Infections

On the basis of our experience with PABA in the treatment of 95 patients with typhus fever and 18 patients with tsutsugamushi disease, we wish to discuss several points of importance in the administration of this substance in human rickettsial infections.

Importance of Early Treatment. Good results are to be expected from PABA treatment only when therapy is begun *early* in the clinical course of typhus fever or tsutsugamushi disease.* The trend in figure 2 suggests that little or no benefit from therapy is likely to be observed when treatment is started after the eighth day of illness. Epidemiologic considerations may be of great value in making a presumptive diagnosis and in starting treatment before the characteristic rash appears or before the usual serologic tests give any help in diagnosis. When the suspicion of a rickettsial infection exists, in the absence of the contraindications mentioned in a later paragraph, we recommend that PABA therapy be initiated without delay.

Optimum Concentration of PABA. It is impossible to state from our clinical experience precisely what the optimum concentration of PABA should be for the various rickettsial infections. Some of the PABA is converted in the body to *para-aminohippuric acid,* which has been found to be entirely inert against *R. prowazeki, R. mooseri,* and *R. orientalis* in experimental infections.[5] Analyses made with Mirick's soil bacillus[20] in a few

* The same statement probably can be made with regard to the use of PABA for Rocky Mountain spotted fever, if, as anticipated, further clinical experience with PABA in that disease is in accord with the results of the therapy of experimental spotted fever in guinea pigs and in embryonated eggs[11, 4] (see addendum).

instances suggested that free PABA accounted for about four-fifths of the diazotizable substances [5] in the serum of patients when the total concentration was 15 to 20 mg. per 100 c.c. It has been observed repeatedly that the minimum concentration of PABA required to achieve inhibition of multiplication in embryonated eggs is approximately 5 mg. per 100 c.c. for *R. prowazeki* and *R. mooseri*, but that a concentration of at least 35 mg. per 100 c.c. is required to inhibit the multiplication of *R. orientalis*.[5]

In the absence of more accurate information, we recommend that sufficient PABA be given to attain promptly, and to maintain thereafter for the entire period of therapy, a blood concentration of PABA (as free diazotizable substance measured against a standard of PABA) of 10 to 20 mg. per 100 c.c. for patients suffering from typhus fever, and 35 to 40 mg. per 100 c.c. for patients suffering from tsutsugamushi disease or Rocky Mountain spotted fever.

Form of PABA. The PABA should be chemically pure, either as the acid or the sodium salt. The pure compounds are almost entirely colorless and odorless in powder form.* In solution a faintly brownish color may be present. At least equimolar amounts of sodium bicarbonate should be given with each dose of the free acid (12.5 c.c. of a 5 per cent solution of sodium bicarbonate for each gram of PABA). The amount of bicarbonate should be increased as required to maintain the urine neutral or alkaline in reaction. In most instances it has been our practice to mix the powder (acid PABA) with 5 per cent solution of sodium bicarbonate at the bedside immediately before each dose. After drinking this mixture the patients received 100 c.c. or more of water.

One of the authors (J. C. S.) with Dr. E. C. Curnen has used a 10 per cent solution of the sodium salt of para-aminobenzoic acid, adjusted to a pH of 7.0 for treatment of a patient suffering from typhus which was contracted in the laboratory. This form of administration eliminated the necessity of mixing the powdered PABA with 5 per cent sodium bicarbonate solution before each dose. The 10 per cent solution of the sodium salt was made up in bulk and stored in the cold. The patient who received this form of therapy decidedly preferred it to the mixture of acid PABA with bicarbonate solution. When sodium para-aminobenzoate solution was administered, no bicarbonate solution was necessary unless the urine became acid.

The Schedule of Dosage. Since PABA is rapidly excreted in the urine it is necessary to administer this drug at frequent intervals throughout the 24-hour period. After many trials the most satisfactory schedule for oral administration was found to be as follows: The initial dose was roughly 0.05 gm. per pound of body weight, i.e., 8 gm. for a patient weighing 160 pounds. This was followed by a dose of 1 to 3 gm. *every two hours day and night* throughout the course of treatment. It is imperative to measure the

* The para-aminobenzoic acid and sodium para-aminobenzoate used for the treatment of the patients considered in this report were obtained by the United States of America Typhus Commission from the Eastman Kodak Company, Rochester, New York.

blood concentration at frequent intervals, particularly in cases where appreciable fluctuations in fluid intake and urine output occur from day to day, or in patients with azotemia. Whenever circumstances permitted, it was our practice to measure the blood concentration every four hours for the first 24 hours of treatment. For determination of blood levels, venipunctures were performed just prior to a dose of the drug, that is, two hours following the last dose. Since the blood concentration rises and falls rapidly after each dose of PABA, measurements of the blood concentration two hours after the previous dose represent the lowest concentrations during that interval. Although in some patients it may be desirable to continue measurements of the blood concentration of the drug at intervals of four hours throughout the course of treatment, this usually is not necessary, provided that renal insufficiency is not present, that the urine output and fluid intake are reasonably constant from day to day, and that the two-hour schedule of dosage is strictly observed. Satisfactory blood levels can be maintained after the first 24 hours of treatment by measuring the blood concentration just before each 8:00 a.m. dose. Evidence obtained in the treatment of experimental rickettsial infections has shown that *the most important factor in successful treatment is the maintenance of the concentration of PABA consistently at or above 10 mg. per 100 c.c. of blood for* R. prowazeki *or 35 mg. per 100 c.c. for* R. orientalis. Because of this fact and because of the rapid elimination of the drug from the body, we advise that frequent determinations be made throughout the entire course of treatment in order to adjust the dosage as required to attain effective blood concentrations.

Parenteral Administration. Injections of 25 c.c. of a 20 per cent solution of sodium para-aminobenzoate in physiological saline adjusted to a pH of 7.0 were given intramuscularly to several patients at intervals of four hours. This solution was sterilized by filtering through a Seitz filter. Determinations of the blood concentration at intervals of two hours in these patients showed somewhat erratic values. This method of administration, although well tolerated, was not considered as successful as the oral route.

The administration of chemically pure sodium para-aminobenzoate in a 2 to 5 per cent solution of physiological saline by constant intravenous drip may be considered for patients who cannot take the drug by mouth. In our experience with four patients at Dachau, when a constant rate of flow over the 24-hour period was achieved, the fluctuation in the blood concentration of the drug was negligible. The rate of flow was adjusted to permit the infusion of 25 to 30 gm. of the drug in 24 hours. The difficulties encountered by the intravenous form of therapy were chiefly those attendant upon any prolonged intravenous infusion under field conditions. Under more satisfactory hospital conditions we believe that the intravenous administration of pyrogen-free buffered solutions of chemically pure sodium para-aminobenzoate would be a valuable adjunct to oral therapy for certain patients.

Duration of Treatment. In the absence of complications arising during treatment, the administration of PABA to patients with rickettsial infections should be continued until the temperature has been normal for at least 48 hours. If the drug is stopped before this time in the treatment of typhus, a secondary rise in temperature lasting from a few hours to several days may be encountered. In the absence of obvious complications this secondary febrile period probably represents a mild recrudescence of the disease. Premature withdrawal of the drug in the treatment of tsutsugamushi disease was followed by the recurrence of fever and characteristic lymphadenopathy.[13]

The Importance of Reaction of the Urine during Treatment. The administration of large amounts of PABA to patients whose urine is acid in reaction may result in precipitation of crystals of PABA in the kidney tubules. Therefore, it must be emphasized strongly that whenever this compound is given, steps must be taken to insure alkaline or neutral reactions in the urine. The pH of the urine should be tested with nitrazine paper at least twice daily as long as patients have measurable concentration of the drug in the blood. Usually it has been found that when 13 to 20 c.c. of a 5 per cent solution of sodium bicarbonate is given with each gram of PABA the pH of the urine will remain at 7.0 or higher. In some cases, however, it may be necessary to increase the amount of bicarbonate solution in order to render the urine neutral or alkaline in reaction. This is particularly the case in patients with azotemia. Under the regimen of bicarbonate administration outlined above, crystals were not found in the urine of patients treated with PABA. Signs of renal involvement, such as azotemia or hematuria, were less frequent and less severe in the treated than in the untreated typhus patients.*

The Treatment of Secondary Bacterial Infections in Patients Receiving PABA Therapy. In our opinion the presence of secondary bacterial infections does not contraindicate PABA therapy. The choice of chemotherapeutic agents for the treatment of complicating bacterial infections during PABA therapy is important. Sulfonamide drugs appear to exert a deleterious effect in experimental rickettsial infections. The action of these drugs on bacteria is inhibited in vitro by the presence of even moderate concentrations of PABA. Sulfonamides should not be employed during the acute febrile phase of the rickettsial disease (first 14 days after clinical onset) or in the presence of measurable concentrations of PABA in the blood. Penicillin is the drug of choice if organisms susceptible to its action are the cause of bacterial infections in typhus or tsutsugamushi disease. Penicillin should be used to supplement but not to replace PABA.

The White Blood Cell Count. The occurrence of leukopenia in some typhus patients treated with PABA makes it necessary to count the white blood cells at frequent intervals during the course of therapy. We recom-

*Two of the authors, C. Z. and N. A. T., observed that the urine of some patients under treatment with PABA contained reducing substances. The significance of this finding was not investigated as a part of the study here reported.

mend that white cell counts be performed on every patient daily from the start of therapy until the third or fourth day after treatment is discontinued. When counts fall below 3,000 the percentage of polymorphonuclear leukocytes should be ascertained.

Contraindications to Treatment with PABA. Until additional experience is gained from the therapeutic use of PABA we suggest that the fall of the white blood cell count below 3,000 per cu. mm., or the reduction of polymorphonuclear cells to less than 25 per cent during treatment be regarded as a contraindication to further therapy. In each case the clinician must decide whether a falling white count is of more serious prognostic import than the withdrawal of the inhibiting effect of PABA on the rickettsiae.

If PABA crystals appear in the urine the administration of the drug should be stopped at once.

Considerable care should be exercised in giving PABA by mouth to patients who are too weak to swallow properly. Aspiration of PABA may be followed by severe tracheobronchitis.

PABA therapy probably is not indicated for typhus patients under 40 years of age who have been adequately vaccinated,[19] except in cases where the clinical condition at the time of hospitalization suggests that they will become severely ill. In cases of suspected tsutsugamushi disease PABA should be administered regardless of a history of previous vaccination, since there is no evidence that vaccines prepared from *R. orientalis* have any effect on the course of the disease in humans.

In our opinion, the presence of renal insufficiency prior to treatment, or its appearance during the course of therapy is not a reason for withholding or discontinuing PABA provided that the blood concentration is determined frequently, that adjustments in dosage are made accordingly, and that the urine is neutral or alkaline in reaction.

Summary and Conclusions

From 1943 to 1945 large amounts of PABA were administered to 95 typhus patients of various nationalities (see footnote on page 2). Twenty of the 95 patients were Egyptian males observed in a controlled study in which treatment was begun before the eighth day of illness. Analysis of the results shows statistically significant differences between the PABA-treated and the untreated groups as regards duration of fever, incidence of complications, and mortality. The evidence suggests that treatment begun early in the first week of illness was more effective than treatment begun late in the first week of illness.

Attention is directed to important points in the use of PABA. The form, route of administration, periodicity of dosage, and duration of treatment are discussed. Emphasis is placed on the importance of attaining promptly and maintaining throughout the course of therapy a concentration of the drug in the blood above 10 mg. per 100 c.c. for *R. prowazeki* and 35

mg. per 100 c.c. for *R. orientalis.* It is stressed that the urine must be kept neutral or alkaline in reaction during treatment. The transient lowering of the white blood cell count observed in some patients was the only definite evidence of toxic reaction to PABA.

The pathologic material from four fatal cases of typhus treated with PABA showed no lesions which were regarded as evidence of poisoning with the drug. One fatal case showed nephrosis of uncertain etiology.

It is pointed out that secondary bacterial infections do not preclude the use of PABA for rickettsial diseases. Penicillin is advocated to supplement PABA in the treatment of secondary infections.

The initiation or continuance of PABA therapy is regarded as contraindicated under the following circumstances: (*a*) if crystals appear in the urine; (*b*) if the white blood cell count falls below 3,000 per cu. mm.; (*c*) if the polymorphonuclear leukocytes are reduced to less than 25 per cent of the total white blood cell count.

Addendum

Four clinical reports on the use of PABA appeared after this manuscript was prepared for publication. Maroney, Davis, and Scott reported successful treatment of one patient with Rocky Mountain spotted fever; Flinn, Howard, Todd, and Scott described 10 patients with that disease who were given PABA with favorable effects in nine cases. Smith reported the use of PABA for 27 cases of murine typhus; Levy and Arnold used PABA for six cases of murine typhus with apparently beneficial results. Woodward (personal communication) has collected data on 15 patients with Rocky Mountain spotted fever who appeared to respond to PABA therapy.

1. Maroney, J. W., Davis, H. C., and Scott, E. G.: Rocky Mountain spotted fever: a case treated with p-aminobenzoic acid, Del. State Med. Jr., 1946, xviii, 104–106.
2. Flinn, L. B., Howard, J. W., Todd, C. W., and Scott, E. G.: Para-aminobenzoic acid treatment of Rocky Mountain spotted fever, Jr. Am. Med. Assoc., 1946, cxxxii, 911–915.
3. Smith, P. K.: The use of para-aminobenzoic acid in endemic (murine) typhus, Jr. Am. Med. Assoc., 1946, cxxxi, 1114–1117.
4. Levy, M. D., and Arnold, W. T.: Para-aminobenzoic acid in treatment of endemic typhus fever, Texas State Jr. Med., 1946, xlii, 314–315. Abstr., Jr. Am. Med. Assoc., 1946, cxxxii, 888.

Appendix

Summary of the important gross and microscopic pathologic findings in three cases of typhus fever treated with para-aminobenzoic acid.

Case 25, Table 6. Gross anatomical diagnosis:*

1. Malnutrition.
2. Congestion of the lungs, bilateral.
3. Myocarditis, acute.
4. Hepatopathy, type to be determined.
5. Nephropathy, type to be determined.
6. Cystitis, acute.

* Autopsy performed by Capt. Ralph M. Schwartz, M.C., Laboratory Officer, 116 Evacuation Hospital, United States Army. Histologic examination of the tissues on cases No. 25, 37, and 38 was done by Capt. Joseph G. Rothenburg, Chief of Pathology, First Medical Laboratory, United States Army.

The *heart* shows a diffuse infiltration of the interstitial tissues by histiocytes, plasma cells, and myelocytes. There is also a diffuse infiltration of epicardial and endocardial tissues. The *liver* shows many areas of focal necrosis occurring in all parts of the lobules, composed of mononuclear cells and nuclear debris. The sinusoids are congested. A large number of convoluted and collecting tubules of the *kidney* are filled with red cells. Some tubules contain pigmented and hyaline casts. The subcapular spaces also contain blood and some are filled with protein precipitate. No inflammatory lesions of the glomeruli are seen. A few foci of lymphocytes are present in the interstitial and perivascular tissues. The head was not examined.

Case 37, Table 6. Gross anatomical diagnosis: †

1. Petechial rash, right axilla and chest.
2. Pulmonary edema.
3. Myocarditis, type and cause undetermined.
4. Lymphoid hyperplasia of mesenteric nodes and gastrointestinal tract.

Sections from the *heart* show a severe degree of inflammatory reaction in the interstitial tissues with lymphocytes, plasma cells, and edema. The myocardial fibers appear atrophic. No vascular lesions of the myocardium are noted. The *lung* parenchyma appears hyperemic, and few intra-alveolar hemorrhages are seen. The small bronchi contain a mucinous exudate in which are pigmented macrophages. The capsular spaces of the *kidneys* contain granules and strands of pink staining material. The cytoplasm of the tubular epithelium appears granular and foamy. The blood vessels are congested. The *brain* shows some degree of satellitosis with infiltration of glial cells. No vascular lesions, petechiae, or foci of necrosis are seen.

Case 58, Table 6. Gross anatomical diagnosis: *

1. Hemorrhages (petechial) in the skin, basal ganglia, renal pelvis, ureters.
2. Myocarditis, acute moderate.
3. Pulmonary tuberculosis with cavitation in right upper lobe, recent, severe.
4. Pulmonary edema, moderate.
5. Atheromatosis of aorta, innominate, subclavian, carotid and coronary arteries, moderate.

The *heart* shows a diffuse infiltration of the interstitial tissues with histiocytes, lymphocytes and plasma cells. The perivascular tissues are but slightly involved. In scattered foci, compression and atrophy of the muscle fibers are present. One arteriole is seen showing inflammatory changes with thrombosis. The *lung* sections show an encapsulated, caseated tuberculous focus. The interlobular septa are thickened and infiltrated with lymphocytes. Areas of intra-alveolar hemorrhage and bronchopneumonia with polynuclear-leukocytic exudate are present. The *liver* sections show sinusoids containing polynuclear leukocytes. The portal triads are infiltrated with lymphocytes and histiocytes. The *kidneys* show isolated foci of interstitial lymphocytic infiltration. The tubular epithelium appears flattened and the cytoplasm granular. The walls of several of the arcuate vessels show invasion by lymphocytes and eosinophiles. The wall of one small artery of the *brain* shows infiltration with mononuclear and polynuclear leukocytes.

Case 13, Table 1. The pathologic findings, gross and microscopic, were typical of typhus fever. The detailed report will appear in another communication by Dr. McAllister.

† Autopsy performed by Capt. William S. Branning, M.C., of the 127th Evacuation Hospital.

* Autopsy performed by Major R. Kimball, First Medical Laboratory, United States Army.

Grateful appreciation is expressed to Dr. S. Burt Wolbach, Shattuck Professor of Pathology, Harvard Medical School, who has kindly reviewed the available microscopic material from Cases 25, 37, and 58. In his opinion the microscopic lesions in the myocardium in all of these cases are typical of louse-borne typhus. No lesions are seen in the liver or kidney which can be ascribed to possible poisoning by para-aminobenzoic acid, with the exception of the kidneys of Patient 25, which show tubular degeneration frequently referred to as nephrosis.

ACKNOWLEDGMENTS

The authors take pleasure in expressing their sincere appreciation to the following members of the United States of America Typhus Commission who helped directly in the work reported in this paper: Brig. Gen. S. Bayne-Jones, Director; Brig. Gen. Leon A. Fox, M.C., Field Director; Lt. Col. David M. Greeley, M.C., AUS; Comdr. W. B. McAllister, Jr., M.C., USNR; Major Robert S. Ecke, M.C., AUS; T_3 L. Stephens; T_3 J. Dworkowitz and T_4 R. Stearman.

The coöperation and assistance of the following persons were of great value in the Dachau Concentration Camp: Col. O. B. Bolibaugh, M.C., C.O. 59 Evacuation Hospital, and Camp Surgeon; Col. A. C. Bradford, M.C., C.O. 127 Evacuation Hospital, and former Camp Surgeon; Col. L. C. Ball, M.C., C.O. 116 Evacuation Hospital; Lt. Col. R. Cohn, M.C., Executive Officer to the Camp Surgeon; Lt. Col. Schrader, Chief, Medical Service, and Lt. Col. Hill, Chief, Surgical Service 116 Evacuation Hospital; and Majors Lipow, B.N. Pease, D. S. Ellis and H. Davis, M.C., 116 Evacuation Hospital; Capt. W. S. Branning, M.C., 127 Evacuation Hospital; Major E. R. Kimball, M.C., and his staff of the 4th Medical Laboratory, United States Army. It is a pleasure to thank Comdr. R. A. Phillips, M.C., for his valuable assistance in the chemical tests. Grateful appreciation is tendered the nurses and corpsmen of the 116 and 127 Evacuation Hospitals who assisted in this work, and to Capt. D. Clark, N.C., and the nurses of the 59 Evacuation Hospital who volunteered for duty on the Typhus Commission Ward.

From Dr. M. A. B. Demerdash Bey, Director of the Cairo Fever Hospital, and other officials of the Egyptian Ministry of Health the authors received valuable assistance throughout the three year period of these studies.

Gratitude is expressed to Dr. Hugo Muench and Dr. Persis Putnam for their help in the statistical analyses.

BIBLIOGRAPHY

1. SNYDER, J. C., MAIER, J., and ANDERSON, C. R.: Report to the Division of Medical Sciences, National Research Council, Washington, D. C., December 26, 1942.
2. HAMILTON, H. L., PLOTZ, H., and SMADEL, J. E.: Effect of p-aminobenzoic acid on the growth of typhus rickettsiae in the yolk sac of the infected chick embryo, Proc. Soc. Exper. Biol. and Med., 1945, lviii, 255–262.
3. GREIFF, D., PINKERTON, H., and MORAGUES, V.: Effect of enzyme inhibitors and activators on the multiplication of typhus rickettsiae: I. Penicillin, p-aminobenzoic acid, sodium fluoride, and vitamins of the B group, Jr. Exper. Med., 1944, lxxx, 561–574.
4. HAMILTON, H. L.: Effect of p-aminobenzoic acid on growth of rickettsiae and elementary bodies, with observations on mode of action, Proc. Soc. Exper. Biol and Med., 1945, lix, 220–226.
5. SNYDER, J. C., and STEVENS, D. A.: Paper in preparation.
6. FOX, J. P., and SNYDER, J. C.: Paper in preparation.
7. SNYDER, J. C., and ZARAFONETIS, C. J. D.: Effects of para-aminobenzoic acid in experimental tsutsugamushi disease (scrub typhus), Proc. Soc. Exper. Biol. and Med., 1945, lx, 115–117.
8. MURRAY, E. S., ZARAFONETIS, C. J. D., and SNYDER, J. C.: Further report on effect of para-aminobenzoic acid in experimental tsutsugamushi disease (scrub typhus), Proc. Soc. Exper. Biol. and Med., 1945, lx, 80–84.
9. ZARAFONETIS, C. J. D., SNYDER, J. C., and MURRAY, E. S.: Immunity following para-aminobenzoic acid therapy in experimental tsutsugamushi disease (scrub typhus), Proc. Soc. Exper. Biol. and Med., 1946, lxi, 240–242.
10. SNYDER, J. C.: Unpublished observations.

11. ANIGSTEIN, L., and BADER, M. N.: Para-aminobenzoic acid—its effectiveness in spotted fever in guinea pigs, Science, 1945, ci, 591–592.
12. YEOMANS, A., SNYDER, J. C., MURRAY, E. S., ZARAFONETIS, C. J. D., and ECKE, R. S.: The therapeutic effect of para-aminobenzoic acid in louse-borne typhus fever, Jr. Am. Med. Assoc., 1944, cxxvi, 349–356.
13. TIERNEY, N. A.: Effect of para-aminobenzoic acid in tsutsugamushi disease, Jr. Am. Med. Assoc., 1946, cxxxi, 280–285.
14. ROSE, H. M., DUANE, R. B., and FISCHEL, E. E.: The treatment of spotted fever with para-aminobenzoic acid, Jr. Am. Med. Assoc., 1945, cxxix, 1160–1161.
15. BAYNE-JONES, S.: The United States of America Typhus Commission, Army Med. Bull., 1943, No. 68: 4–15.
16. TIERNEY, N. A., and YEOMANS, A.: Metabolic studies in louse-borne typhus, Jr. Clin. Invest., in press.
17. FISHER, R. A.: Statistical methods for research workers, 1936, Oliver and Boyd, London, Sixth edition, pp. 100–102.
18. YEOMANS, A., CLEMENT, D. H., ZARAFONETIS, C. J. D., PHILLIPS, R. A., and SNYDER, J. C.: Activities of the U. S. A. Typhus Commission at Dachau Concentration Camp, 10 May to 10 June 1945, Report to the Director of the U. S. A. Typhus Commission.
19. ECKE, R. S., GILLIAM, A. G., SNYDER, J. C., YEOMANS, A., ZARAFONETIS, C. J. D., and MURRAY, E. S.: The effect of Cox-type vaccine on louse-borne typhus fever, Am. Jr. Trop. Med., 1945, xxv, 447–462.
20. MIRICK, G. S.: The oxidation of p-aminobenzoic acid and anthranilic acid by specifically adapted enzymes of a soil bacillus, Jr. Exper. Med., 1943, lxxviii, 255–272.

REPORT OF AN OUTBREAK OF Q FEVER AT THE NATIONAL INSTITUTE OF HEALTH. I. CLINICAL FEATURES *

By CHARLES G. SPICKNALL,† M.D., ROBERT J. HUEBNER,‡ M.D., JAMES A. FINGER,† M.D., and WILLIAM P. BLOCKER,§ M.D.

AT the end of the first week of February 1946, a febrile illness began to appear among the workers in Building No. 5 * of the National Institute of Health where research was being done on the rickettsia of Q fever. Eighteen cases occurred in an explosive manner between February 6 and February 11, 1946. By May 31 the total number of cases reached 47. This paper deals with the clinical characteristics shown by 45 of the 47 cases.

Epidemiological [1] and laboratory [2] aspects of the outbreak are considered in the other papers in this series. The recent report of a number of cases of Q fever in packing houses, stockyard, and railroad employees in Texas,[3] the identification of a disease occurring widely in certain populations of Italy [4] and the Balkan States [5] as Q fever, and the report of a case from Panama [6] indicate that the illness is more prevalent than has been generally recognized.

This disease was first described in 1937 by Derrick [7] as occurring among meat workers in Brisbane, Queensland, Australia. The clinical features of the nine cases reported were sudden onset, severe headache, slow pulse rate, and normal white cell count. Pneumonitis was not described in these patients. A rickettsia was isolated from these cases and given the name of *Rickettsia burneti* [8] by Derrick.

In 1938, Davis and Cox [9] reported the isolation of a filter-passing infectious agent from *Dermacentor andersoni* collected in Montana. Cox [10] described the rickettsia-like characteristics of the organism and suggested the name *Rickettsia diaporica* [11] for the organism and the name American Q Fever [12] for the disease. The clinical features of a case contracted in a Montana laboratory [13] were similar to those described in Australia and those reported below. *Rickettsia diaporica* and *Rickettsia burneti* were found by Burnet and Freeman,[14] and Dyer [15] to be immunologically indistinguishable.

Burnet and Freeman [16] described a series of mild or subclinical laboratory infections with the rickettsia of Q fever. Hornibrook and Nelson [17] reported a series of cases in 1940 in which a pneumonitis was recognized for the first

* Received for publication November 9, 1946.

From the National Institute of Health, Bethesda, Maryland, and The U. S. Public Health Service Dispensary, Washington, D. C.

† Surgeon, U. S. Public Health Service.

‡ Senior Assistant Surgeon, U. S. Public Health Service.

§ Assistant Surgeon, U. S. Public Health Service.

* Building No. 5 is one of 8 buildings which house the Bethesda laboratories of the National Institute of Health. In this building are the Division of Infectious Diseases, Division of Biologics Control, and a dental unit of the Division of Physiology.

time. The similarity of these cases to those now called primary atypical pneumonia was pointed out by Dyer, Topping, and Bengtson.[18] The pathology of this illness was described by Lillie, Perrin and Armstrong.[19]

The diagnosis of Q fever was made during the 1946 outbreak when either of the two following criteria was fulfilled:

1. A rise in titer for Q fever in the complement fixation test during the convalescent stage of the illness.

2. When no sera were obtained during the acute stage of the illness, a strongly positive reaction for Q fever in the complement fixation test during the convalescent stage of the illness was considered as confirming the diagnosis. Most of the cases fulfilled the first criterion. A few patients who were suspected of having Q fever did not develop significant titers in the complement fixation test and have not been included in this study.[1]

Fifteen cases were hospitalized and thoroughly studied. The remaining 30 cases could not be as thoroughly studied; however, all but a few had histories, physical examinations, and complement fixation reactions during the acute stage of the illness and chest roentgen-rays and laboratory studies during their convalescence.

The incubation period ranged from 12 to 23 days.[1] Cases occurred in all categories of the personnel working in Building No. 5. There were 13 women and 32 men in the series studied; their ages were from 18 to 64.

One of the features of the illness was definite prodromal symptoms lasting in most cases one-half to one day. These symptoms were headache, malaise, generalized aching, anorexia, nausea, vomiting, chest pain, backache, and burning of the eyes. One patient gave a history of headache for three weeks, cough for two weeks, malaise for five days, and burning of his eyes for four days prior to the onset of his fever. The symptoms in some of the cases with prolonged prodromata could have been caused by unrelated upper respiratory infections. Headache, malaise, and aching were the most common prodromal symptoms.

According to the clinical findings, the 45 patients can be divided into two groups: (1) 13 cases with clinical or roentgen-ray evidence of pneumonitis or with symptoms suggesting pneumonitis; (2) 32 cases without clinical or roentgen-ray evidence of pneumonitis or without symptoms suggesting pneumonitis. In the latter group the severity of the disease varied markedly. Six of the patients continued work because of the mildness of their symptoms or because they disregarded more severe symptoms. Three of the patients without pneumonitis were hospitalized, one of whom had a moderately severe form of the disease.

As in the previously reported cases,[7] headache was a prominent symptom. It was most commonly frontal and some patients also complained of occipital headache which was accompanied, in several cases, by stiffness of the neck. In none of the patients was this sign marked enough to indicate a lumbar puncture. The headache was variously described as "severe," "pounding,"

and "bad." There was often increase in the severity of the headache during coughing. One patient stated that it felt like the "top of my head was coming off when I coughed." Chills, chilly sensations, fever, and often sweating occurred in a large number of patients. As in cases previously reported,[7] some of the sweating might have been caused by antipyretics. The highest recorded temperature after a chill was 106° F. Fever occurred in a few cases without chills or sweats. The fever lasted from one to 15 days, the average being about six days. Three patients apparently had no fever.

TABLE I

Tabulation of Symptoms and Signs in 45 Cases of Q Fever

Symptoms	
Headache	34
Generalized aching	20
Cough	15
Chest pain or discomfort	12
Nausea and/or vomiting	10
Burning of eyes and/or lacrimation	6
Bloody sputum	5
Abdominal pain	3
Diarrhea	2
Constipation	2
Epistaxis	2
Sensitivity of skin	1
Signs	
Chills or chilly sensations (often accompanied by sweating)	32
Râles	11
Fever without chills or sweating	10
Bronchial or bronchovesicular breathing	5
Conjunctivitis	5
Dullness on percussion	4
Increased vocal fremitus	4
Dyspnea	3
Cyanosis	2
Delirium	2
Rash	1
Incontinence	1
Decubitus ulcers	1

Generalized aching was a prominent complaint and was more pronounced in the lower extremities. Cough occurred in all the patients with pneumonitis. Five patients had frankly bloody sputum, which was not observed in previously reported cases.[17] There were no patients in the series who had "rusty" or "prune juice sputum."

The chest pain was described as substernal discomfort or burning or more severe pain on coughing or deep inspiration over the lower lateral chest wall.

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, or constipation were not infrequent. The only complaints of one patient without pneumonitis were nausea, vomiting, diarrhea, and a dull frontal headache. As in Derrick's cases,[7] burning of the eyes, lacrimation, and conjunctival injection were found in a few patients.

Physical signs of pneumonitis, such as dullness on percussion, râles, bronchial breathing, etc., were easily detected in most of the patients with pulmonary involvement. A few of the pneumonitis cases could not be differentiated clinically from lobar pneumonia. Bradycardia, although present in some cases, was not constant, and was thought to be of no value in differential diagnosis. The spleen was not palpable in any case.

Routine laboratory studies were not particularly helpful. Most of the patients on whom blood counts were obtained had a normal white blood cell count and differential, although one patient with evidence of pneumonitis had a count as high as 18,000 with 86 per cent neutrophiles. In general, the sedimentation rate was moderately increased during the febrile course of the illness, but returned to normal when the patient recovered. Sputum smears and cultures showed staphylococci, *Streptococcus viridans,* or a few pneumococci that could not be typed. Albuminuria occurred in the patients who had high temperatures and cleared up after the temperature returned to normal.

Chest roentgen-rays in the pneumonitis cases were similar to those described by Hornibrook and Nelson.[17] In a few cases the consolidation observed was like that of lobar pneumonia; the changes in other cases could not be differentiated by roentgen-ray from those caused by atypical pneumonia. Electrocardiograms taken on one patient during the course of his illness and on six patients during their convalescence were normal.

Many patients complained of aching of the legs and thighs for variable periods after apparent recovery from the illness. A few continued to have this symptom as long as three months. Fatigue was another common complaint and lasted in a few cases as long as one month. One patient had an acute thrombophlebitis of the leg during convalescence from his illness. One patient was rehospitalized for a probable thrombophlebitis following her discharge from the hospital; however, further observation revealed no evidence of venous thrombosis.

Various diagnoses by various physicians were made in this group of patients before the true nature of the illness was recognized. In the milder cases the most common diagnosis was influenza. Without serological studies or animal inoculations it would be difficult to make a differential diagnosis between influenza of a mild type and less severe cases of Q fever. During the outbreak, illnesses occurred in the personnel of Building No. 5 which were clinically indistinguishable from serologically established cases of Q fever but which, on repeated tests, showed a negative reaction in the complement fixation test for Q fever. The incidence of these and other acute respiratory illnesses in Building No. 5 during the outbreak was found to be similar to that in a comparable group outside this building.[1] Because of the headaches, some patients were thought to have sinusitis. Two cases of malaria were thought at first to be Q fever because of the chills, fever, sweating, and headaches. One patient was treated for rheumatic fever at first, as her prominent symptoms were pains in the extremities. The diag-

nosis of typhus fever was considered in one case because of the macular rash which resembled that of typhus. In contrast to other rickettsial diseases such as Rocky Mountain spotted fever, scrub typhus, and epidemic typhus, relatively mild cases of Q fever were not unusual in the older age groups and despite two critical cases, there were no fatalities.

The diagnosis of Q fever was confirmed in all cases by the complement fixation test, using antigens prepared from the American and Italian strains of rickettsia. The technic employed in the test was described by Bengtson.[20] The Italian Q antigen was found to be the more sensitive. The highest serum titers with this antigen on specimens taken during or after the illness ranged from 1:16 to 1:4096. With the American Q antigen the titers ranged from 1:4 to 1:512. Organisms identified as *Rickettsia burneti* were isolated from the whole blood of five cases and from the sputum of one.[2] Four of 45 convalescent sera tested failed to react with the American antigen, though they reacted to the Italian antigen.

In general, the sera tested by complement fixation were negative until 10 to 14 days after the onset of the illness. In many of the patients the diagnosis of the illness was not established until clinical recovery had occurred. There was no correlation between the severity of the illness and the complement fixation titer. The highest titer for both the antigens was found in a patient who continued working throughout a mild attack of the illness (Case No. 9).

Other serological studies were done on many cases, including complement fixations for spotted fever, endemic typhus, and psittacosis, with negative results. Weil-Felix agglutinations with Proteus OXI9, OX2, and OXK were negative.

Penicillin and sulfadiazine were given to a majority of the patients having the more severe form of the illness, with the result that neither good nor ill effects were apparent. Three patients were given blood transfusions. Two of these received immune blood from donors who had the illness in the 1940 outbreak.[17] There appeared to be no definite improvement following this therapy. One patient was placed in an oxygen tent for about one week, which relieved his dyspnea. In general, the treatment was symptomatic and in the more severe cases supportive.

Case Reports

The following cases are reported as examples of patients with mild and severe forms of the illness and of patients with and without pneumonitis:

Case 16: A severe case with pneumonitis, white male, age 42. On February 11, 1946, the patient had sudden onset of chills and fever and nausea and vomiting. His symptoms continued and he was admitted to the hospital on February 14. On admission, his temperature was 104.6° F., pulse 120, and respirations 25. Soon after admission his temperature rose to 106° F. (figure 1). His face was flushed, his sensorium was clear, and there was no dyspnea nor cyanosis. The left side of the chest

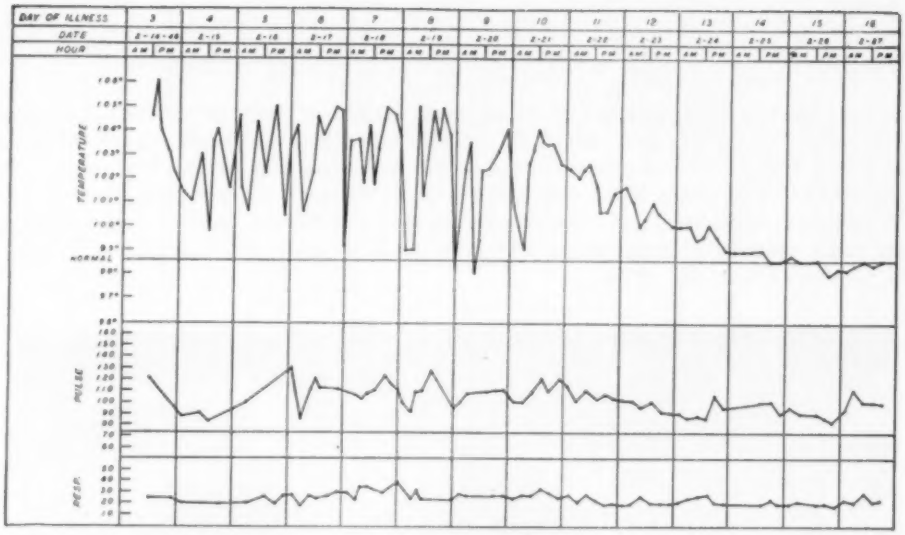


FIG. 1. Case 16.

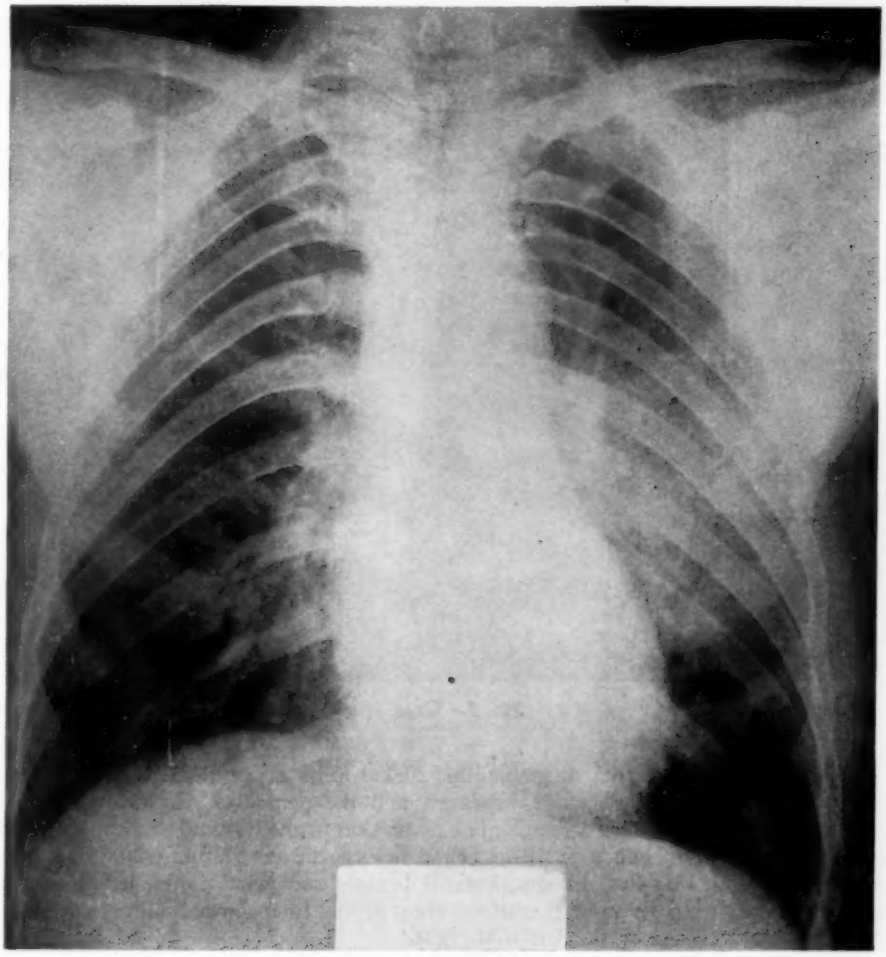


FIG. 2. Case 16.

showed decreased excursion and there were crepitant râles in the left mid-chest anteriorly. There was generalized abdominal tenderness. Roentgen-ray of the chest showed a heavy mottled consolidation in the lower portion of the left upper lobe (figure 2). The white blood cell count was 13,200 with 72 per cent neutrophiles, 25 per cent lymphocytes, and 3 per cent monocytes. Urinalysis showed 2 plus albumin and many coarsely granular casts. *Streptococcus viridans* and *Staphylococcus albus* were cultured from the sputum.

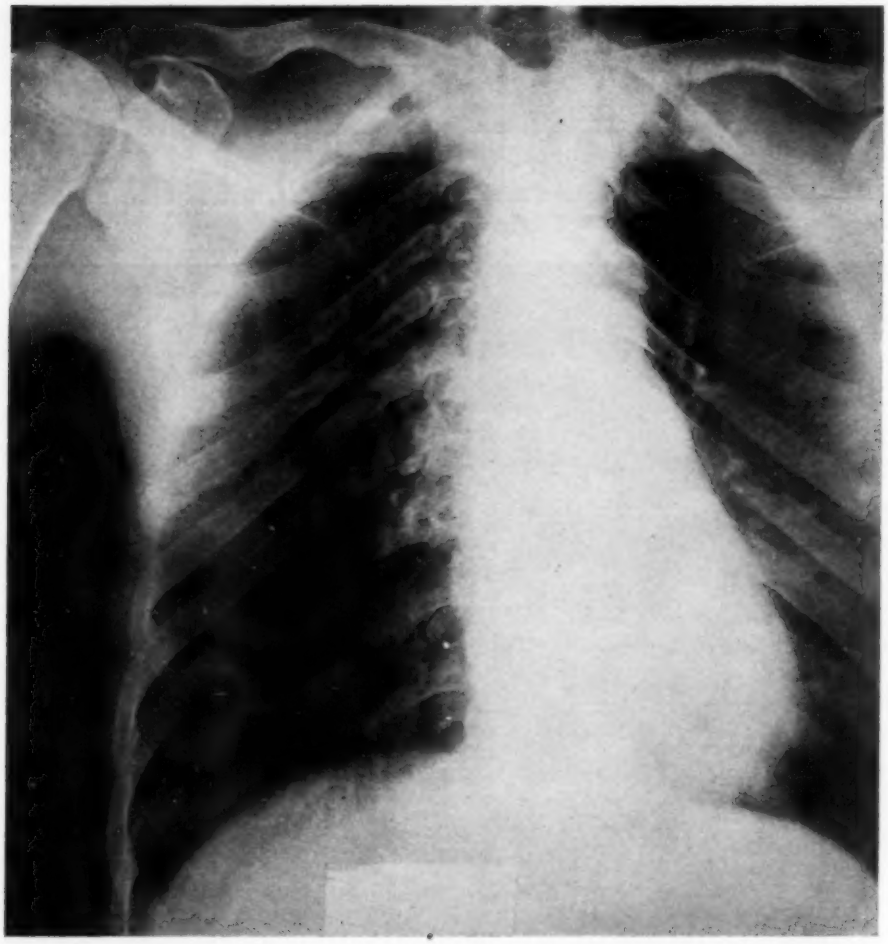


FIG. 3. Case 16.

The patient was started on penicillin, 20,000 units every three hours intramuscularly. He showed no response, however, and the penicillin was discontinued on February 19. He developed a cough after admission to the hospital and this gradually became worse until on February 18 he began to expectorate sputum containing bright red blood. About this time his respirations became somewhat rapid, but he did not complain of dyspnea. Examination of the chest at this time showed dullness, bronchial breathing, and râles over the left mid-chest.

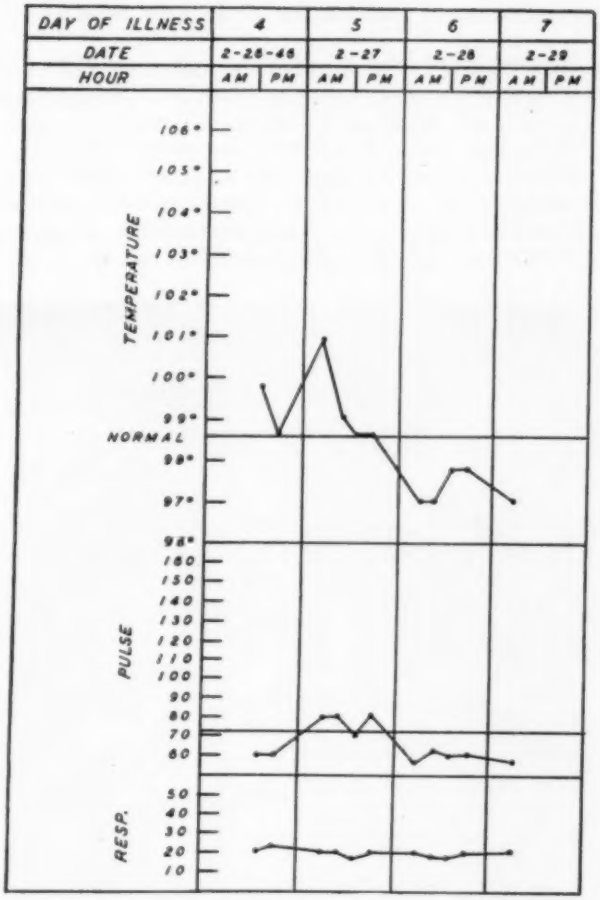


FIG. 4. Case 31.

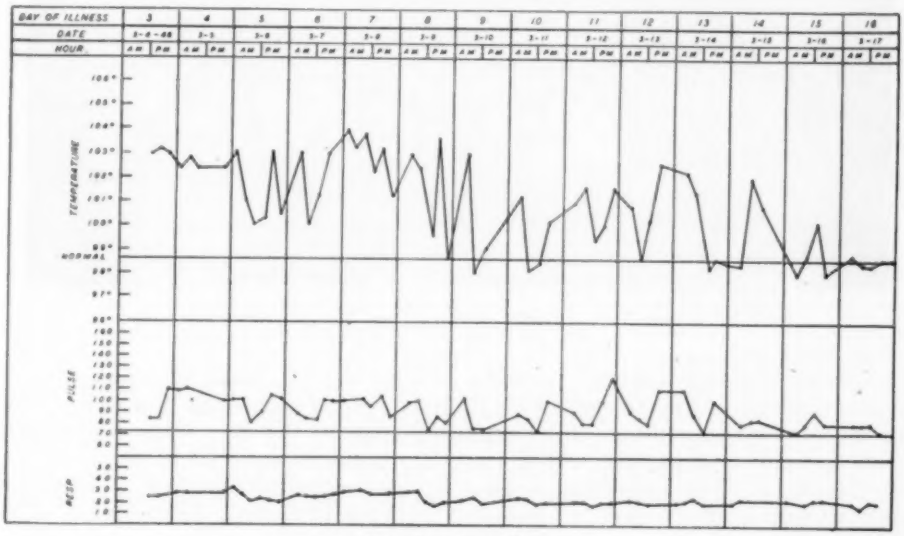


FIG. 5. Case 31.

Oxygen therapy with a tent was tried but the patient refused to stay in the tent. On February 19 his white cell count was 12,300 with 85 per cent neutrophiles. On February 20 his icterus index was 8 and the non-protein nitrogen was 25 mg. per cent. On February 21 the serum albumin was 3.51, serum globulin 2.58, malaria smear negative, hemoglobin 74 per cent, red cell count 4,250,000 and white cell count 9,000 with 82 per cent neutrophiles. The patient's condition continued to be poor. He had two severe episodes of epistaxis, was weak, and mentally clouded. He was given intravenous fluids, two transfusions, and sulfadiazine, one gram every four hours.

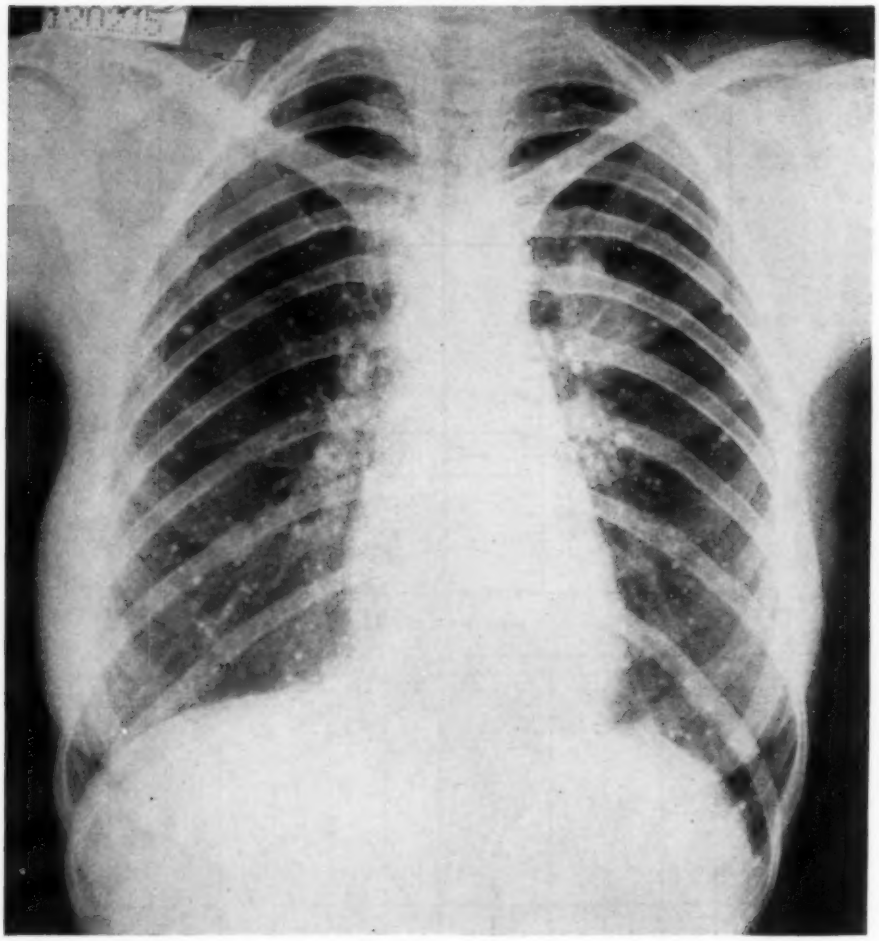


FIG. 6. Case 26.

The sulfadiazine was continued until the fifteenth day of illness, by which time the patient's fever had returned to normal by lysis and his cough had disappeared. He continued to have a rapid pulse. Electrocardiogram at this time was within normal limits except for tachycardia. At no time did the patient complain of headache. On March 3 acute thrombophlebitis of the left lower extremity developed. This complication responded very well to lumbar sympathetic injection. Roentgen-ray of the chest on March 19 showed scant mottling of the left mid-lung (figure 3).

On February 15 and February 19, the complement fixation test for Q fever was negative. On February 25, it was positive 1:512 with the American antigen, and greater than 1:512 with the Italian antigen.

Case 23: A mild case without pneumonitis, white male, age 29. On February 23 this patient complained of a malaise and anorexia. The evening of that day he had chills and fever, a severe frontal headache, and mild substernal pain; a slight cough developed later. On February 25 his afternoon temperature was 102° F. The next day he was admitted to the hospital. Physical examination was negative on

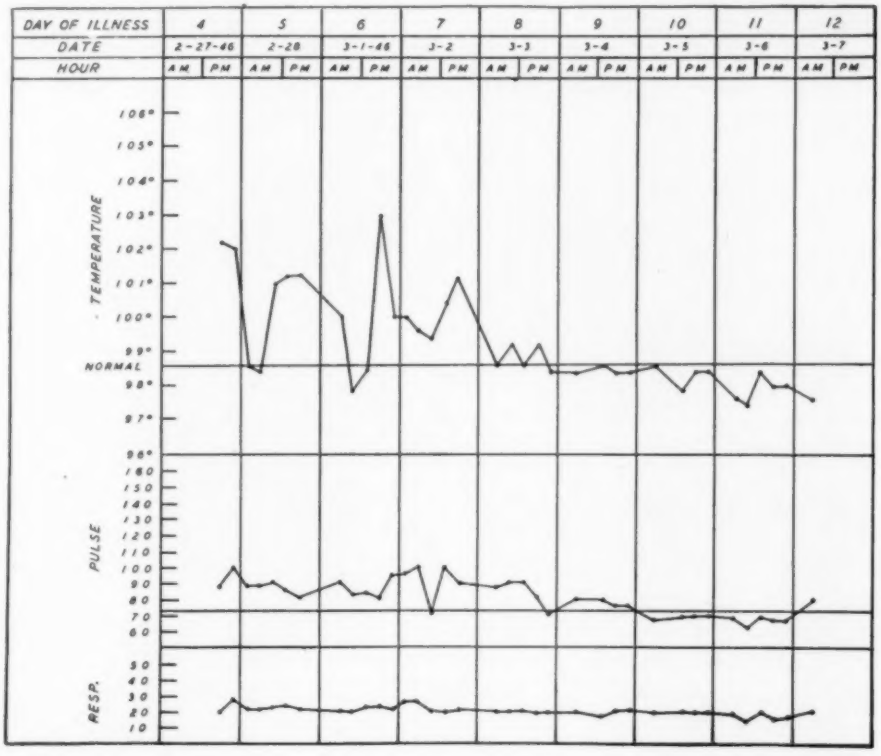


FIG. 7. Case 26.

admission except for a temperature of 99.8° F. (figure 4), and his symptoms had cleared up. Roentgen-ray of the chest was negative. On February 27 his white cell count was 5,500 with 74 per cent neutrophiles, 24 per cent lymphocytes, and 2 per cent monocytes. On February 28 his temperature remained normal and on March 1 he was discharged from the hospital. On March 15 he returned to work but continued to complain of some fatigue until the latter part of March.

On February 28 complement fixation for Q fever was negative with both the Italian and American antigen. On March 6 his serum was positive 1:128 with the Italian antigen, and 1:16 with the American. On April 8 the titers were 1:16 with the Italian and 0 with the American antigen.

Case 31: A severe case without pneumonitis, white male, age 58. On March 1, 1946, this patient began to have anorexia, malaise and headache. On March 2 he had chills and fever and severe frontal and occipital headache. He was admitted to the

hospital on this date. He gave a history of a chronic cough with copious expectoration of mucopurulent sputum for years.

Physical examination on admission showed an acutely ill, drowsy patient whose temperature was 103° F., pulse 85, respirations 25. His chest was emphysematous and there were musical and crackling râles at both lung bases. Roentgen-ray of the chest showed generalized bronchitic changes and thickened pleura at both costophrenic angles. His sedimentation time was 16 mm. in one hour, hemoglobin 85 per cent,

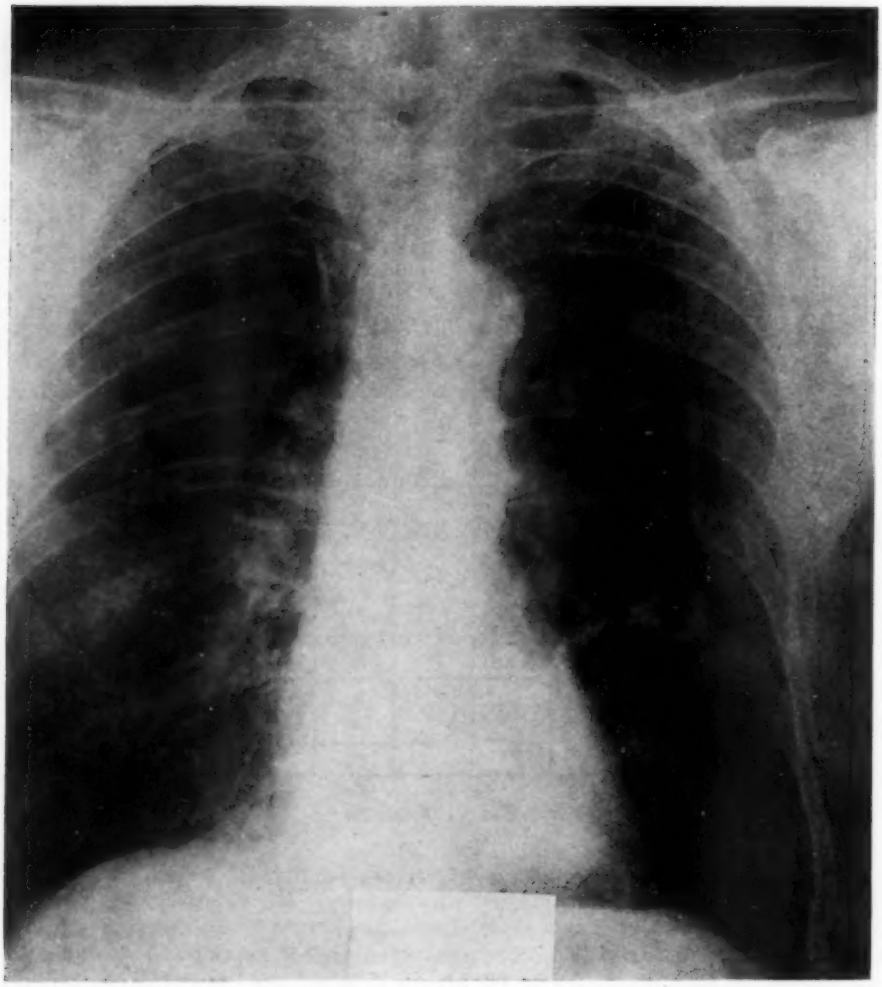


FIG. 8. Case 9.

red cell count 5,100,000, white cell count 6,700 with 79 per cent neutrophiles, 11 per cent lymphocytes, and 10 per cent monocytes. Urinalysis showed a specific gravity of 1.022 and was otherwise negative.

Throughout the course of his illness the patient complained of headache, substernal pain, and generalized aching. On March 9 he received a transfusion of immune blood without noticeable effect. His treatment was otherwise symptomatic.

Roentgen-ray of the chest on March 9 showed no change, and the patient continued to have a normal white cell count and normal urinalysis. On March 13 he was found to have skin lesions on his chest, abdomen, and arms. The lesions were dull red macules 2 to 5 millimeters in diameter and blanched on pressure. The rash resembled that of typhus and gradually faded until it had disappeared on March 19.

The patient continued to have fever until March 17 (figure 5). On May 13 he was still complaining of pains in the legs. On March 8 complement fixation with the Italian antigen was negative; on March 14 the titer was greater than 1:512. On April 10 his serum was positive with the Italian antigen in a titer of 1:256, and with the American, 1:512.

Case 26: A moderately severe case with pneumonitis, white female, age 33. On February 22 the patient had generalized aching, malaise, and headache. These symptoms continued until February 24 when she had chills, fever, and sweating. The following day she began to have rather severe pain in both lower extremities, burning of the eyes, and lacrimation. On February 27 she was admitted to the hospital. Physical examination on admission showed a rather drowsy patient whose temperature was 102.2° F., pulse 90, and respirations 20. There were no chest signs nor other findings. Roentgen-ray of the chest showed a small homogenous consolidation extending upward and outward from the left hilus. There were many fine discrete calcifications in both lungs (figure 6). The urinalysis was negative. The hemoglobin was 80 per cent, red cell count 4,450,000, white cell count 5,600 with 60 per cent neutrophiles, 1 per cent eosinophiles, 1 per cent basophiles, 31 per cent lymphocytes, and 7 per cent monocytes.

The patient's symptoms and fever continued until March 3 (figure 7). Roentgen-ray of the chest on March 7 showed marked improvement and was negative except for calcifications on March 14. Treatment was symptomatic. She was discharged from the hospital on March 7 and was readmitted for probable thrombophlebitis on March 18. No evidence of this complication was found and she was discharged on March 25. She returned to work on April 8, but when last seen on May 12 was still complaining of pains in the lower extremities.

On March 5 the complement fixation titer with the Italian antigen was greater than 1:512, and with the American, 1:256. On April 8 both gave titers of 1:128.

Case 9: A mild case without pneumonitis, white male, age 60. On February 8 this patient had sudden onset of vomiting and diarrhea and a dull frontal headache. Following this he felt as though he had a fever for two or three days. He continued working, however. Roentgen-ray of the chest on March 18 showed some increase in the lung markings but was otherwise negative (figure 8). He complained of a headache until March 8.

On February 18 complement fixation with the Italian antigen was negative. On February 28 and March 28 the titer was 1:1,024 with the same antigen. The titer with the American antigen on February 28 was 1:128.

Summary

1. Forty-five of 47 cases of Q fever occurring during a laboratory outbreak were studied from a clinical standpoint.

2. Pneumonitis was not the predominant clinical characteristic of this outbreak, although it was shown to be present in 13 of the cases.

3. In many of the pneumonitis cases the lung lesions were easily found by physical signs. Bloody sputum was observed in five of these patients.

4. Mild cases occurred. The difficulties in making a differential diagnosis are pointed out. In this respect the value of a sensitive and accurate

method of making a diagnosis, such as is provided by the use of the Italian antigen in serological tests, is apparent.

5. Penicillin, sulfadiazine, and transfusions of immune blood were found to have no definite effect on the course of the disease.

BIBLIOGRAPHY

1. Huebner, R. J.: Report of an outbreak of Q fever at the National Institute of Health. II. Epidemiological features. (To be published.)
2. Huebner, R. J., and duBuy, Herman: Report of an outbreak of Q fever at the National Institute of Health. III. Laboratory and certain experimental epidemiological features. (To be published.)
3. Irons, J. V., Topping, N. H., Shepard, C. C., and Cox, H. R.: Outbreak of Q fever in the United States, Pub. Health Rep., 1946, lxi, 784–785.
4. Robbins, F. C., and Ragan, C. A.: Q fever in the Mediterranean area: Report of its occurrence in American troops. I. Clinical features of the disease, Am. Jr. Hyg., 1946, xliv, 6–22.
5. Commission on Acute Respiratory Diseases. Identification and characteristics of the Balkan grippe strain of *Rickettsia burneti*, Am. Jr. Hyg., 1946, xliv, 110–122.
6. Cheney, G., and Geib, W. A.: The identification of Q fever in Panama, Am. Jr. Hyg., 1946, xliv, 158–172.
7. Derrick, E. H.: Q fever, a new fever entity: clinical features, diagnosis and laboratory investigation, Med. Jr. Australia, 1937, ii, 281–289.
8. Derrick, E. H.: *Rickettsia burneti*, the cause of Q fever, Med. Jr. Australia, 1939, i, 14.
9. Davis, G. E., and Cox, H. R.: A filter-passing infectious agent isolated from ticks: isolation from *Dermacentor andersoni*, reaction in animals and filtration experiments, Pub. Health Rep., 1938, liii, 2259.
10. Cox, H. R.: A filter-passing infectious agent isolated from ticks: description of organism and cultivation experiments, Pub. Health Rep., 1938, liii, 2270.
11. Cox, H. R.: Studies of a filter-passing infectious agent isolated from ticks: further attempts at cultivation on cell-free media: suggested classification, Pub. Health Rep., 1939, liv, 1822.
12. Cox, H. R.: *Rickettsia diaporica* and American Q fever, Am. Jr. Trop. Med., 1940, xx, 463.
13. Dyer, R. E.: A filter-passing infectious agent isolated from human ticks. IV. Human infection, Pub. Health Rep., 1938, liii, 2277.
14. Burnet, F. M., and Freeman, M.A.: A comparative study of rickettsial strains from an infection of ticks in Montana and from Q fever, Med. Jr. Australia, 1939, ii, 887.
15. Dyer, R. E.: Similarity of Australian Q fever and a disease caused by an infectious agent isolated from ticks in Montana, Pub. Health Rep., 1939, liv, 1229.
16. Burnet, F. M., and Freeman, M. A.: Note on a series of laboratory infections with the rickettsia of Q fever, Med. Jr. Australia, 1939, i, 11–12.
17. Hornibrook, J. W., and Nelson, K. R.: An institutional outbreak of pneumonitis. Epidemiological and clinical studies, Pub. Health Rep., 1940, lv, 1936.
18. Dyer, R. E., Topping, N. H., and Bengtson, I. A.: An institutional outbreak of pneumonitis, isolation and identification of causal organism, Pub. Health Rep., 1940, lv, 1946.
19. Lillie, R. D., Perrin, T. L., and Armstrong, C.: An institutional outbreak of pneumonitis. Histopathology in man and rhesus monkeys in the pneumonitis due to the virus of Q fever, Public Health Rep., 1941, lvi, 149–155.
20. Bengtson, I. A.: Complement fixation in rickettsial diseases. Technique of test, Pub. Health Rep., 1944, lix, 402–405.

THE CLINICAL SIGNIFICANCE OF DIVERTICULOSIS, INCLUDING DIVERTICULITIS, OF THE GASTROINTESTINAL TRACT*

By EMILE C. NASH and WALTER LINCOLN PALMER, *Chicago, Illinois*

THE frequency of diverticula in various portions of the gastrointestinal tract necessitates a careful interpretation of their significance, symptoms and treatment. They may occur with no symptoms whatsoever, or they may be solely responsible for the complaints of the patient. At times their differentiation from neoplasm and other serious organic conditions may be most difficult.

Diverticula are blind sacs with small necks lined by mucosa and opening into the gastrointestinal tract. The exact nature of their pathogenesis is not completely understood. As a rule they seem to result from congenital weakness of the wall, or from inability of the muscular layers to withstand the intraluminal pressure to which they are constantly subjected. Diverticula are found in all portions of the digestive tract—most commonly in the colon, not infrequently in the esophagus, stomach, duodenum and small intestine. The first descriptions were those of Sommering in 1794 and Cruveilhier in 1849.[1]

ESOPHAGUS

In a monograph on diseases of the esophagus, Zenker and Ziemssen in 1877 classified esophageal diverticula into the pulsion and traction types—a classification in practical use today.[2] The pulsion type occurs at the lower portion of the pharynx and is, thus, frequently referred to as the pharyngo-esophageal, or Zenker's diverticulum. The so-called traction diverticulum most frequently develops in the region of the left main bronchus or near the cardia.

PULSION DIVERTICULA

The pharyngo-esophageal diverticulum is a true herniation of the mucosa and sub-mucosa through the fibers of the inferior constrictor muscles of the pharynx as they run transversely or through the obliquely dividing fibers of the cricopharyngeus muscles on the posterior aspect of the esophagus. As these muscles spread off to become longitudinal and envelope the esophagus, they leave on the posterior wall an area weakly supported by muscularis. In the course of many years, the intraluminal pressure produces the formation of a diverticulum (figure 1).

* Presented at the Twenty-Seventh Annual Session of the American College of Physicians, Philadelphia, May 16, 1946.

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

The symptoms are directly referable to the act of swallowing. Careful inquiry usually reveals that the dysphagia is first noticed with dry foods. It increases gradually in magnitude until finally water and other liquids are regurgitated. In two of our cases the obstruction was so marked that a loss of weight of 20 and 40 pounds respectively developed within a few months.

There is a definite relationship between the symptoms and the size of the sac.[3] During the earliest stages there is simply a projection of the mucosa and sub-mucosa through the fibers of the crico-pharyngeus muscle and no

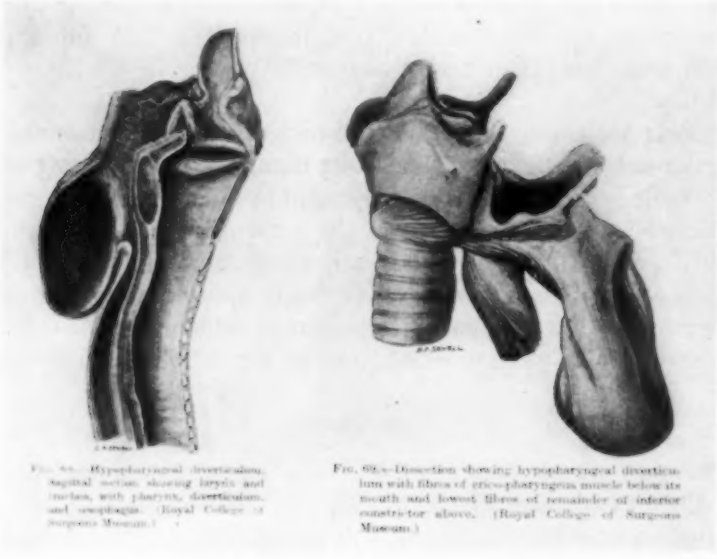


FIG. 1. Pulsion diverticulum (from Abel [7]).

sac is actually present. Dry particles of food may lodge in this projection. When a small sac actually forms there is then a regurgitation of mucus with food eaten previously. Eating and swallowing are frequently associated with gurgling which becomes particularly bothersome to the patient. When the sac enlarges, descends into the mediastinum and causes an angulation of the esophagus obstructive symptoms ensue.

In diagnosis the history is far more important than the physical examination: Roentgen-ray demonstrates the diverticulum easily. Esophagoscopy is seldom necessary. The following case is illustrative:

L. T., a 54 year old female, complained of difficulty in swallowing and of a choking sensation in the chest for two years. There had been some nausea and vomiting during this period. The patient stated that the dysphagia was noted with solid food only at first and that by massaging the throat the food could be made to pass. The dysphagia became progressively worse and by the time she was seen in the clinic, considerable trouble was encountered in swallowing liquids. The physical

and laboratory examinations were normal. Roentgenography revealed a large pharyngo-esophageal diverticulum. The sac was excised by two-stage operation with complete symptomatic relief (figure 2, left).

Nicolodoni, in 1877, has been credited with the first operation, although Wheeler is said to have performed the first successful one.[2] In all of the surgically treated cases reviewed by us recovery has been uneventful and with complete relief of the symptoms. The two-stage operation appears to

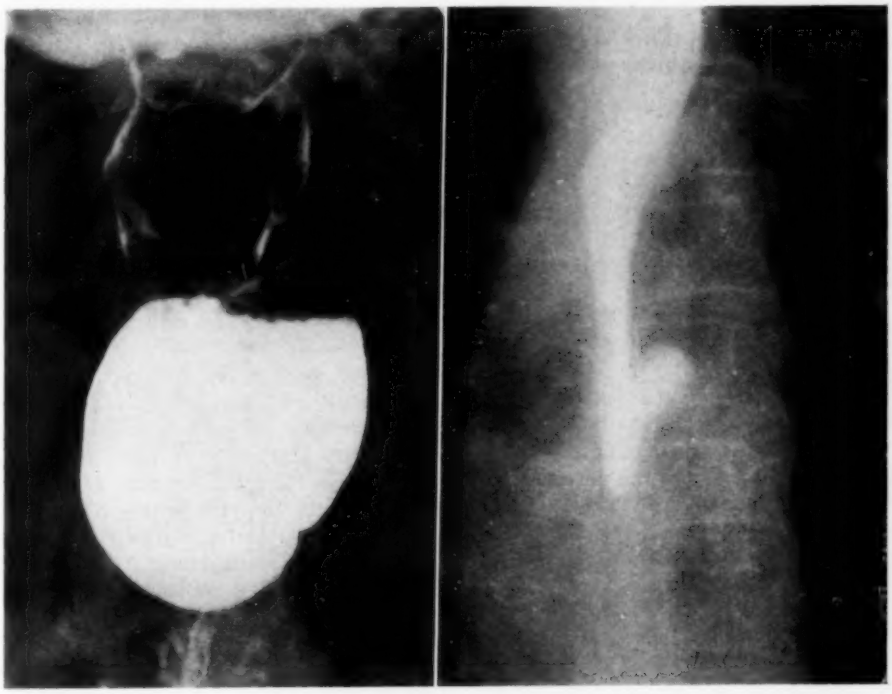


FIG. 2. (left) Pulsion diverticulum of the pharynx. (right) Traction diverticulum of the esophagus.

be the procedure of choice. The mortality rate is lower and there is less danger of mediastinitis. In 1939 Lahey [5] reported 104 such operations with only one death.

TRACTION DIVERTICULA

Of 20 traction diverticula selected at random from the clinic files 10 were located in the mid-portion of the esophagus near the bifurcation of the trachea and 10 near the cardia. In seven of the 20, the presenting symptoms were fairly typical of the associated organic disease: cholelithiasis 2, gastric ulcer 2, duodenal ulcer 1, and carcinoma of the stomach and pleural effusion each 1. In five of these the symptoms subsided after institution of therapy

for the organic condition; the other two came to the clinic for diagnosis only and hence were not followed. In eight cases the diverticula represented accidental findings in patients with functional bowel distress; the symptoms subsided with appropriate therapy. In the remaining five cases there was no evidence of a co-existing disease. The symptoms referable to the esophagus were substernal burning, discomfort after eating and intermittent dysphagia. In each instance the symptoms improved with reassurance, the use of a bland diet, and the prescription of belladonna and phenobarbital. Some recurrence of symptoms was noted in one or two patients but not in the others. Symptoms such as these are seen quite frequently in patients without esophageal diverticula and without other organic disease. We have not been able to associate traction diverticula with any definite symptomatology. The following cases are illustrative:

E. W., a 65 year old female, complained of nervousness, cramps in the arms and legs, and headaches of indefinite duration. There were no esophageal symptoms. The physical examination was essentially normal. The traction diverticulum noted roentgenologically in the lower esophagus was considered of no clinical significance (figure 2, right).

A. K., a 53 year old male, entered the hospital on July 16, 1941, complaining of a period of gnawing epigastric pain of seven years' duration. The pain was of the ulcer type occurring approximately two hours after meals. He also mentioned the fact that for many years there had been some difficulty in swallowing his food completely. The physical examination disclosed tenderness in mid-epigastrium. The maximum gastric acidity (histamine) was 116. Roentgen-ray revealed a pyloric ulcer with deformity of the antrum and spectacular esophageal diverticula (figure 3). At operation on July 21, 1941, a duodenal ulcer was found for which a posterior gastroenterostomy was performed. Recovery was uneventful and the patient was discharged with instructions to continue medical ulcer management. He has remained free of symptoms and has not experienced any significant difficulty in swallowing.

There are autopsy records of traction diverticula associated with such complications as mediastinal abscess, bronchial fistula and pulmonary gangrene. Moersch and Finney [6] in a review of 39 cases of esophago-tracheobronchial fistula found two (5 per cent) arising from a traction diverticulum in the middle third of the esophagus near the tracheal bifurcation. These must be considered as rarities not of much significance in the routine practice of medicine.

Gastric Diverticula

Gastric diverticula are also thought to arise either from pulsion or traction. About 65 per cent of them occur near the cardia.[8] In a large series of stomachs examined roentgenologically by Reich,[8] diverticula were found in less than one half of 1 per cent. Martin [9] analyzed 103 uncomplicated cases of pulsion diverticula; 63 were located in the cardia, 11 in the mid-portion and 14 in the prepyloric area along the lesser curvature; nine occurred along the greater curvature; five in the mid-portion and four in the prepyloric area; six were miscellaneous.

The roentgenologic detection of diverticula of the upper end of the stomach may be difficult and require careful search in various positions.[10] Gastroscopy may confirm the diagnosis and aid in the differentiation of diverticulum-like formation occurring secondary to perforating peptic ulcer or carcinoma[11]; in the typical lesion at the cardia gastroscopy gives very little information and may even be dangerous.

G. D., a 43 year old female, complained of nausea, burning epigastric pain and constipation for one year. The symptoms had appeared following the death of her mother from cancer and persisted through the illness of her son with rheumatic fever.

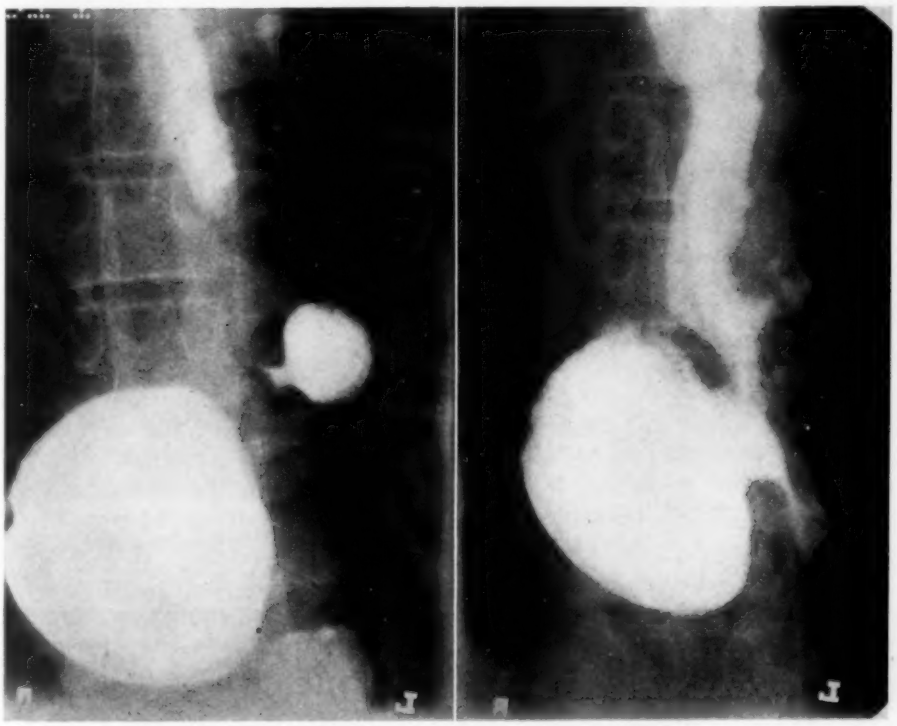


FIG. 3. Multiple traction diverticula of the esophagus.

Roentgenograms were reported to have disclosed either a diverticulum or an ulcer near the cardia. The roentgenologist was said to have advised immediate operation; the local physician prescribed a bland diet with antacids. The patient experienced some relief, but she was confused by the conflicting advice and continued to worry about her condition. Our examination elicited the above information and disclosed a normal physical and laboratory examination except for the demonstration of a histamine-fast achlorhydria. The presence of a gastric diverticulum was established roentgenologically (figure 4). The nature of the lesion was explained to the patient in detail with firm reassurance. The constipation was treated with a diet and antispasmodics. Marked improvement ensued. The patient's own conclusions were as follows: "I think I overworked, worrying about my son, my husband, and my mother dying of cancer. I built up a complete anxiety neurosis without intending

to do so and then I went to the doctor. The x-ray man found the diverticulum and advised me to have an immediate operation. The doctor treated me and I worried."

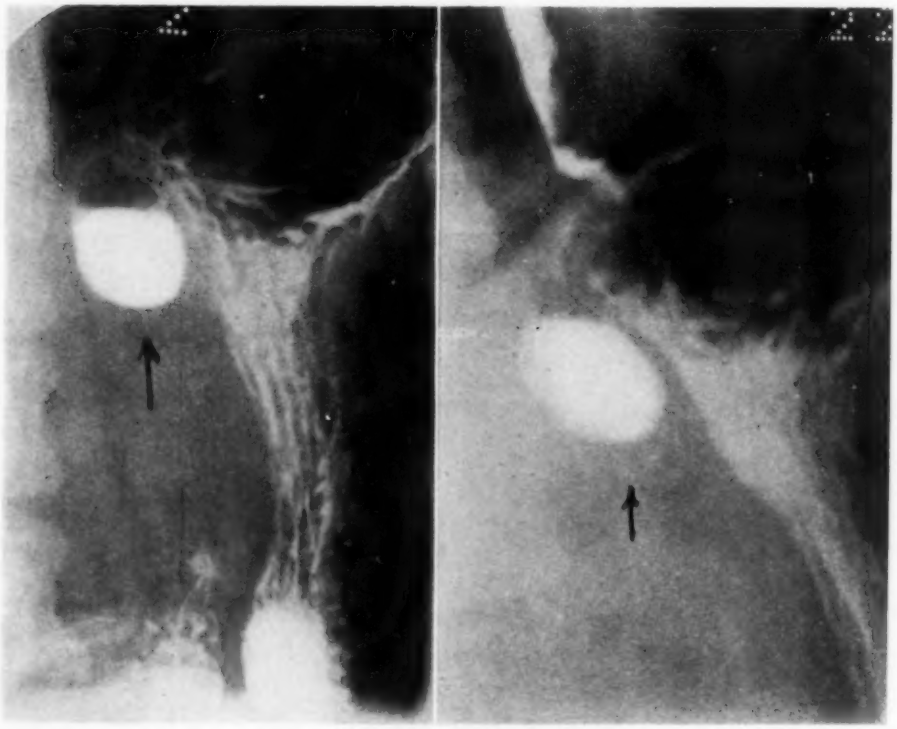


FIG. 4. Gastric diverticulum.

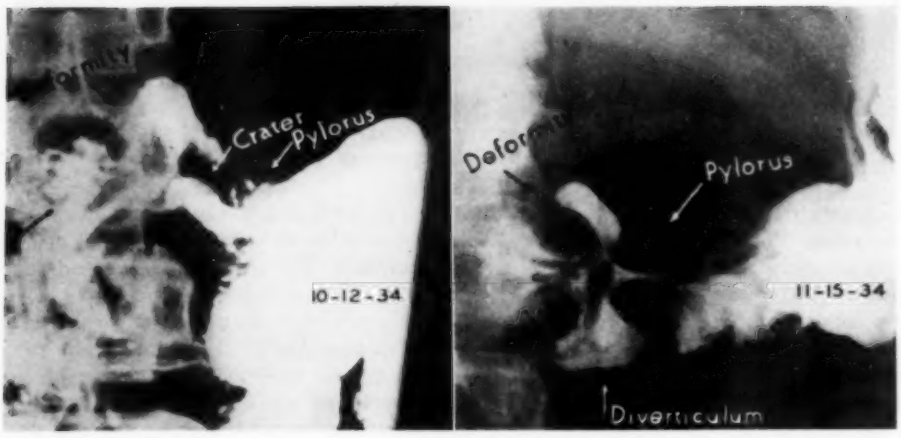


FIG. 5. Duodenal ulcer with crater (left hand view) and bilateral contracture of a large bulb with resultant pseudodiverticula formation proximal to the deformity.

Duodenal Diverticulae

Priority in the description of duodenal diverticula has been erroneously credited to Morgagni (1765) and to Sommering (1794). The first case was described by Chomel in 1710.[13] The pouch was apparently secondary to a cholecysto-duodenal fistula, for it contained "twenty-two stones of yellow color with smooth polished surfaces." These lesions were then looked upon as surgical curiosities. Virchow, Grases, and Fisher during the latter part of the last century gave accurate anatomic descriptions, and the papers of W. J. Mayo, Beer, Moynihan, Drummond, Mummery and others brought out their clinical significance.[14] Since the publications of Odgera (1929) and Edwards (1935), duodenal diverticula have generally been classified as primary or congenital, and those secondary to duodenal ulcer. Some authors have listed vaterine diverticula as a special type because of the sequelae occasionally seen.

One of the chief problems in connection with duodenal diverticula is the differentiation of the congenital diverticulum and the pseudodiverticulum produced by a chronic ulcer with much scarring. Congenital diverticula are very rare in the first portion of the duodenum, the duodenal bulb, whereas almost all of the ulcer diverticula occur in this area.

A. B., a 40 year old male giving a history of a periodic epigastric distress of the ulcer type of 10 years' duration, was found on roentgen-ray examination (figure 5) to have a high-grade deformity of the duodenal bulb with crater formation and two pseudodiverticula formed by the scarring from the ulcer. After the crater of the ulcer had disappeared or become very much smaller the deformity of course persisted as did the pockets on either side of the bulb between the pylorus and the deformity—the classical pseudodiverticula produced by the hour glass contracture of the bulb. The gastric free acidity (Ewald) was 45.

Lesions at the apex of the bulb may be either diverticula or ulcer; indeed the differentiation may be impossible until response to treatment has been observed.

A 47 year old male, A. C., was seen because of burning and pressure beneath the sternum for three weeks. The patient had been treated for 12 years for chondrosarcoma of the left iliac bone. The burning discomfort appeared in the afternoon, late evening and occasionally about 4 or 5 a.m. It was never present in the forenoon. The maximum gastric free acidity (histamine) was 108 clinical units. A roentgen-ray examination revealed a collection of barium interpreted as a diverticulum of the second portion of the duodenum (figure 6). The distress was completely relieved by ulcer management. A second roentgen-ray study three weeks later disclosed a marked decrease in the size of the presumed diverticulum; a third examination some weeks later showed its complete disappearance and thus proved that the original lesion had in fact been a peptic ulcer.

For all practical purposes neoplastic ulceration does not need to be considered in the differential diagnosis of lesions in the bulb but it does require consideration in those of the second, third and fourth portions. The roent-

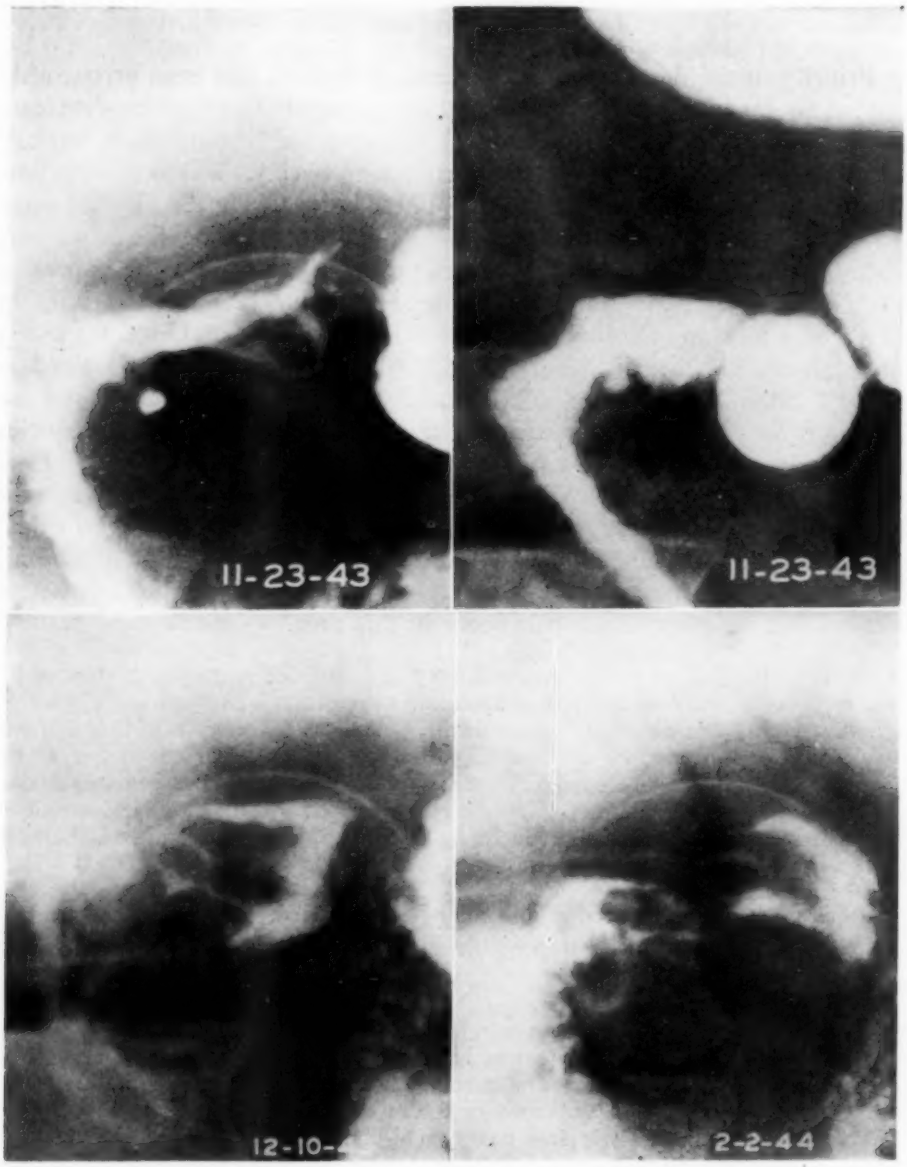


FIG. 6. Duodenal ulcer simulating diverticulum of the second portion of the duodenum. The crater disappeared on ulcer management.

genologic manifestations are usually clear cut and are associated with loss of appetite, loss of weight and occult blood in the feces.

In our experience it has rarely been necessary to pay any attention to duodenal diverticula. The symptoms are usually due to organic disease elsewhere, such as duodenal ulcer or cholelithiasis, or to a functional dis-

turbance. Relief is obtained with appropriate therapy and without regard to the diverticula.

S. B., a 55 year old male, had been perfectly well except for three attacks of typical biliary colic. Roentgen-ray disclosed a faint visualization of the gall-bladder with two diverticula of the second portion of the duodenum (figure 7). At operation

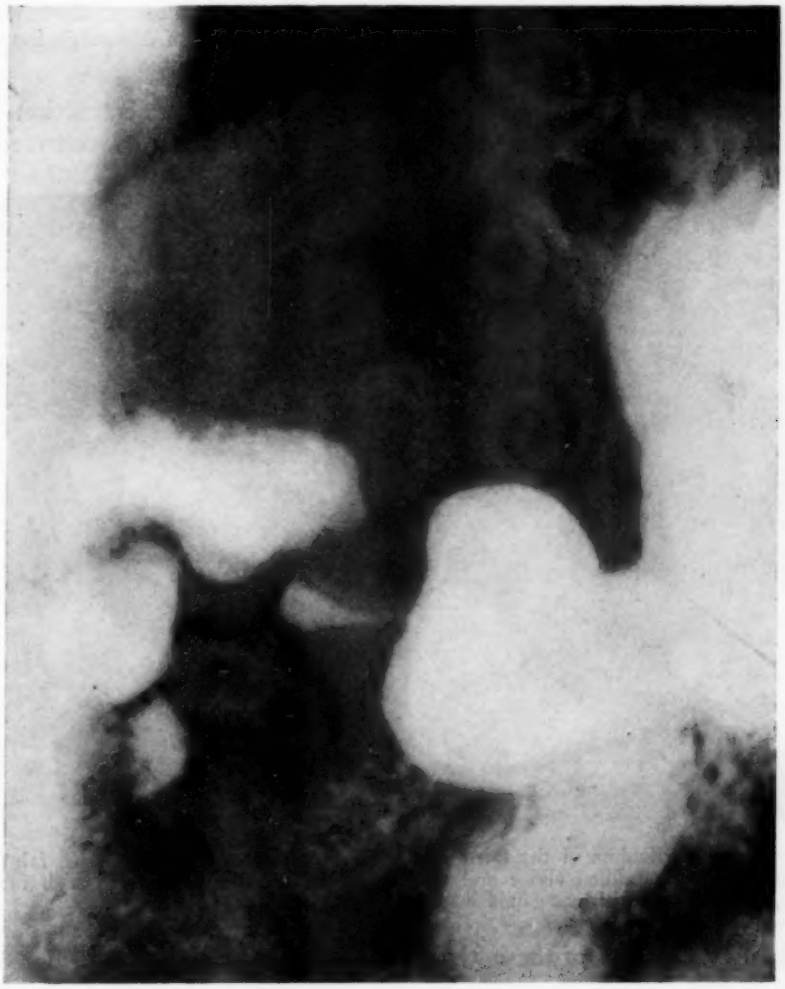


FIG. 7. Multiple diverticula second portion of duodenum.

a gall-bladder containing both sand and stones was found and removed. The symptoms were relieved.

In three of our cases of duodenal diverticula obstructive manifestations were present; resection of the lesion gave complete relief of the symptoms in two; the third experienced a stormy postoperative period and died.

G. G., a 57 year old male, complained of umbilical pains appearing several hours after meals and relieved by milk and food. For the past year he had experienced nausea and vomiting four to 10 times weekly. There had been a weight loss of 12 pounds in the last six months. The only significant finding during physical examination was tenderness about the umbilicus. The urinalysis and blood count were normal. Gastroduodenal roentgenograms revealed a large diverticulum in the third portion of the duodenum (figure 8). Laparotomy on November 9, 1944, confirmed the roentgenographic findings; the diverticulum was excised. Postoperative recovery was complicated by right lower lobe pneumonia. At the time of discharge the patient was completely relieved of his digestive symptoms.

Another rare complication of duodenal diverticula is obstruction of the pancreatic ducts with pancreatic necrosis. Ogilvie in 1941 collected four

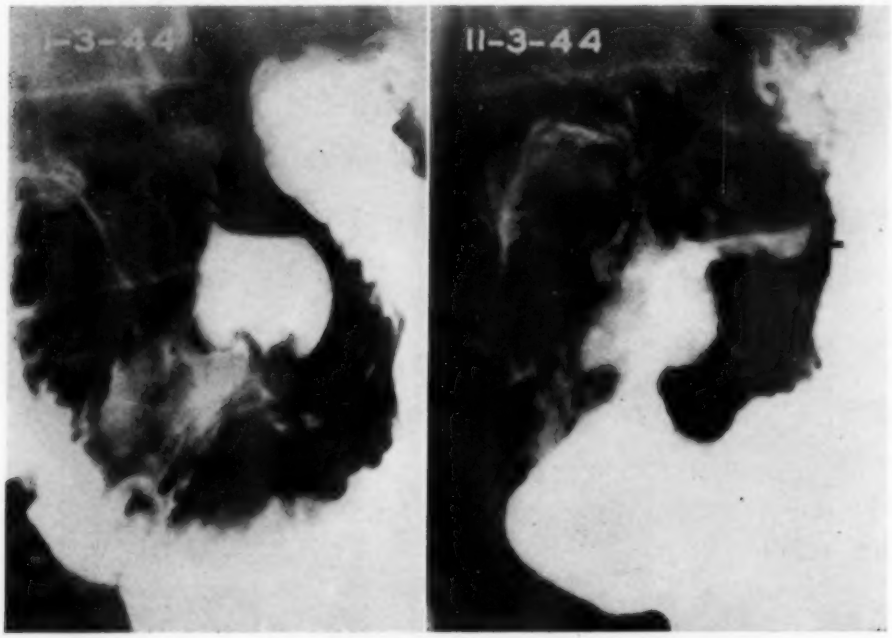


FIG. 8. Diverticulum of the third portion of the duodenum. On the left, faint outline of bulb, diverticulum filled above and to the right. In right hand view, bulb filled with barium, diverticulum with gas (fluid level present).

such cases. In three of these, the pancreatic ducts were described as dilated.

Duodenal diverticula rarely become inflamed, probably because of three factors: (1) the sterility of their contents, (2) their retro-peritoneal position, and (3) their inverted position and wide ostia.[12] On the other hand the ostium is often concealed among the plicae circulares of the duodenum and the wall of the sac contains little or no muscle. Case found that while the average emptying time of the sac in 18 consecutive cases was 11 hours, barium was not uncommonly retained beyond 48 hours and in one case for seven days. Such retention is not a serious matter and does not warrant operation.

Basset (1907), Rosenthal (1908) and Bauer (1912) apparently reported the first cases of acute diverticulitis of the duodenum.[12] Perforation is a rare sequela; Beaver [19] described an instance in 1938 and found in the English literature only three other cases. Boland [22] stressed the fact that the symptoms simulate perforated peptic ulcer and urged that if the operation reveals nothing more than an exudate along the anterior duodenal wall an incision should be made in the posterior peritoneum to search for a perforated diverticulum. Peri-diverticulitis is also a rare sequela.[24]

In spite of the fact that Chomel in 1710 in describing the first diverticulum recorded the presence of gall stones within it, enteroliths are nevertheless uncommon. Harris [20] (1932) during an operation on a 49 year old female discovered a peri-vaterine diverticulum containing a large, annular stone consisting mainly of cholesterol.

Apparently the only reported instance of carcinoma in association with a duodenal diverticulum is described by Morrison and Feldman.[27]

The advisability of surgical treatment in most duodenal diverticula is highly questionable.[21] Complications such as hemorrhage and diverticulitis are very rare. Operation is usually technically rather difficult and extensive. It is much wiser to try a medical regimen based on a conservative diet and the use of antispasmodics, reserving operation for the exceedingly small group of patients with definite and persistent inflammation. Pain and tenderness are not in themselves conclusive evidence of diverticulitis, for other conditions such as a duodenal ulcer or a tender colon may account for these manifestations.

Jejunum

Diverticula are found less frequently in the jejunum than in any other portion of the gastrointestinal tract. Case [24] in reviewing the literature from 1854 to 1920 was able to collect only 17 non-Meckelian diverticula in either the jejunum or ileum at operation or necropsy. However by 1938 the number had increased to 187.[25] In only 12 of these was there acute inflammation or perforation. Diverticula may occur in any portion of the circumference of the bowel, but most of them are located near the mesentery or between the leaves of the mesentery. They may be multiple or single, large or small. They are usually discovered accidently at operation, autopsy or by roentgen-ray. When uncomplicated they are rarely if ever responsible for the patient's symptoms and require no treatment. The complications of non-Meckelian diverticula of the small bowel are similar to those of Meckel's diverticula although much more rare.[26] Treatment is indicated for the complications only, primarily intestinal obstruction or acute diverticulitis.[27]

Meckel's Diverticulum

Meckel's diverticulum occurs as a result of incomplete obliteration of the omphalo-mesenteric duct, its structure depending on the degree of obliteration. The diverticulum is usually situated on the anti-mesenteric side of

the ileum, 30 to 90 cm. proximal to the ileo-cecal valve. In rare instances it may occur at any point between the stomach and the colon.[28] It may be attached to other viscera, or to the abdominal wall; rarely it is located between the leaves of the mesentery.[29] The size of the opening into the ileum is important because when the opening is wide it permits the unhindered entrance and exit of intestinal contents. However, this wide neck may also permit the lodgement of a large variety of foreign bodies. The incidence of Meckel's diverticulum is 1.5 to 3 per cent of all persons, the frequency being twice as great in males as in females.[28]

The symptoms depend primarily on the nature of the complication present, obstruction and inflammation being the most frequent ones in adults, peptic ulcer with hemorrhage the most common one found in children. The acute catarrhal, phlegmonous, and gangrenous forms of diverticulitis occur, complicated by perforation with abscess formation or peritonitis. The symptoms are so similar to those of acute appendicitis that the diagnosis is rarely made prior to operation although a peri-umbilical location of the pain and tenderness is suggestive of diverticulitis. The treatment is, of course, operation with surgical removal.

The frequency with which Meckel's diverticula are the cause of intestinal obstruction is rather surprising. Miller and Wallace found 63 instances of intussusception in 201 cases of Meckel's diverticula found at operation. Harkins [36] found such diverticula to be responsible for 2 per cent of all cases of intussusception. Intestinal obstruction may also result from adhesions about a diverticulum.

Peptic ulcer is the most frequent complication of Meckel's diverticulum.[30, 32, 33] The presenting symptom in 81 per cent of such cases is intestinal hemorrhage.[32] The bleeding is often profuse and persistent. The pathogenesis of these ulcers has been clearly established pathologically and experimentally. They are found only in diverticula containing ectopic gastric mucosa the incidence of which has been estimated as 16 per cent.[29] There have been numerous theories to explain the presence of these aberrant elements, the most commonly accepted one being that of Albrecht who maintains that the entodermal lining of the primitive intestinal tube possesses the potentiality of developing into any of the glandular components of the fully developed gastrointestinal tract.[28] The ectopic gastric mucosa contains acid and pepsin secreting glands; the presence of acid secretion has been demonstrated.

J. W., a 17 year old male, complained of intermittent pain in the abdomen and marked muscular weakness for three years. The pain was described as a knife-like sticking sensation in the region of the umbilicus somewhat to the left of the mid-line. Pain was most apt to occur from one half to three quarters of an hour after the noon and evening meals. . Physical examination revealed marked pallor and a palpable spleen. Laboratory examinations revealed a profound secondary anemia and the persistent presence of occult blood in stools. Prior to operation two blood transfusions of 500 c.c. each were given. Following the second transfusion, the patient

suddenly developed symptoms suggesting an internal hemorrhage and later passed a stool containing a large amount of liquid and clotted blood. At operation an inflammatory mass was found in the ileum about 40 cm. from the cecum. A section of ileum, approximately 60 cm. in length, containing the mass was resected. The resected ileum contained a Meckel's diverticulum about 4 cm. in length and completely surrounded by an inflammatory mass (figure 9, top). Near the entrance of the

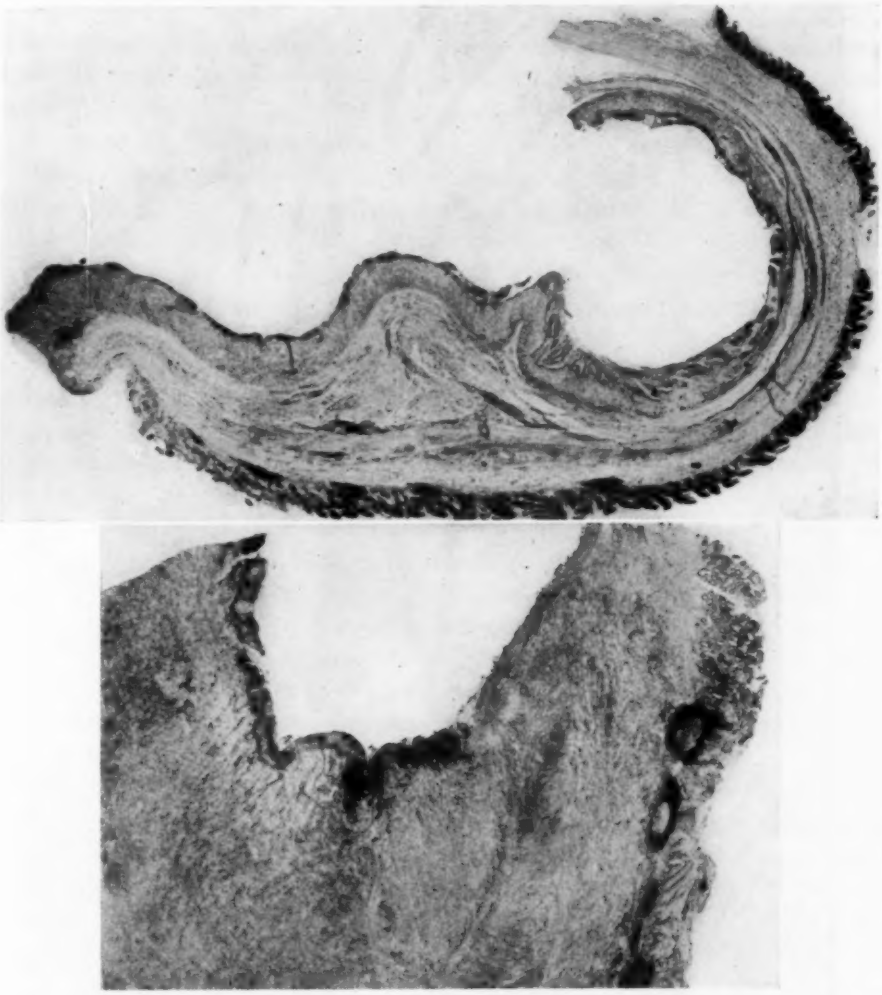


FIG. 9. (above) Longitudinal section of Meckel's diverticulum lined with gastric mucosa and surrounded by jejunal mucosa—reduced from magnification 10 × (kindness Dr. Lester Dragstedt). (below) Gastric ulcer at the mouth of Meckel's diverticulum—reduced from magnification 20 × (kindness Dr. Lester Dragstedt).

diverticulum was a round perforated ulcer approximately 1.5 cm. in diameter (figure 9, bottom). Histologic examination disclosed gastric mucosa lining the entire diverticulum (figure 10). The ulcer had penetrated the mucosa, sub-mucosa and muscularis and produced a marked inflammation in the serosa.

FIG. 10. Gastric mucosa lining Meckel's diverticulum—reduced from magnification 125 × (kindness Dr. Lester Dragstedt).

Dragstedt and Matthews have produced similar lesions experimentally by allowing the acid gastric juice from a Pavlov pouch to drain into a blind loop of small intestine.

A malignant tumor of Meckel's diverticulum is rare enough to be called a pathological curiosity.[35] Nygard and Walters [35] in 1937 made a survey of 20, six carcinomas and 14 sarcomas. In one of these an adenocarcinoma had developed in heterotopic gastric mucosa.

Colon

Diverticula of the colon, as in all other parts of the digestive tract, have been classified as true or false, congenital or acquired. Congenital true diverticula involving all layers of the intestinal wall are seen occasionally but the vast majority of colonic diverticula are formed by the herniation of the mucosa through the muscular layers.[38] Neither autopsy nor roentgen-ray studies have given as yet the true incidence in the various age groups.[39, 37, 40] The term diverticulosis denotes simply the presence of diverticula. Clinical manifestations appear only when secondary inflammation develops,[41] diverticulitis. Diverticulitis seems to be caused chiefly by fecalith obstruction of the neck which prevents adequate drainage and leads to pressure necrosis.[37] The inflammation may progress until the mucous membrane within the diverticulum undergoes atrophy with subsequent round cell infiltration of the submucosa followed by ulceration and perforation.[37] Extension of the process can result in chronic thickening of the wall.

The symptoms of diverticulitis of colon are variable. There may be a single acute attack of pain, usually in the left lower quadrant lasting from one or two days to several days or even longer depending upon the complications present. There may be several such recurring attacks.

Brown and Marcley [42] reported that during the period from 1919 to 1929 in the Mayo Clinic, 277 cases of diverticulitis of the colon were treated medically; 99 (26 per cent) were subjected to operation at some time or other. The following case demonstrates the manner in which sufficient progress may be obtained under medical management.

C. W., a 63 year old female, complained for three weeks of acute attacks of lower abdominal cramp-like pain. Stools were of normal shape and color. Physical and laboratory examinations were normal. Roentgen-ray revealed diverticulosis and chronic diverticulitis of the sigmoid (figure 11, right). Treatment consisted of mineral oil and a bland diet. For the past four years the patient has gotten along very well although she has experienced transitory abdominal discomfort from time to time.

Usually the differentiation between diverticulitis and carcinoma is easy; it is difficult in a few cases, and occasionally it is almost impossible.[42] Diverticulitis may produce a stony-hard fixed mass quite indistinguishable on rectal examination from inoperable carcinoma. Carcinoma, like diverticulosis, is most commonly found in the sigmoid or descending colon. There is no satisfactory evidence that diverticulosis is a precursor of cancer.[42] The daily passage of gross red blood per rectum is always suggestive of carcinoma although it may result from hemorrhoids alone or from non-specific ulcera-

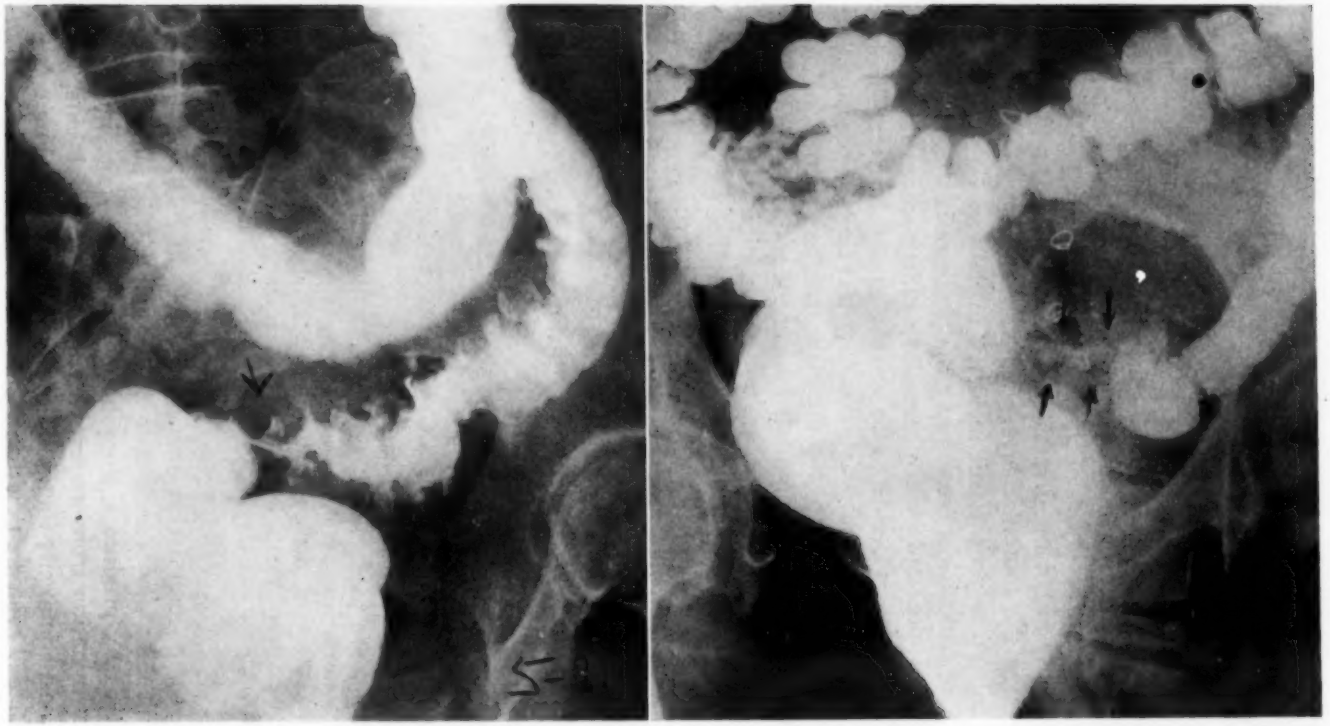


FIG. 11. Chronic diverticulitis of sigmoid responding satisfactorily to medical management (four years). (right) Chronic diverticulitis simulating carcinoma of the sigmoid.

tive colitis; in our experience rarely if ever is bleeding to be attributed to diverticulosis or to diverticulitis. The roentgenologic differential diagnosis depends on the fact that carcinoma tends to destroy the mucosa and to produce a margin in which no mucosal pattern can be seen whereas in diverticulitis the mucosal patterns persist and are usually exaggerated.

The following cases are illustrative of the difficulty in differentiation and also of some of the indications for surgical therapy.

L. S., a 47 year old female, complained of three attacks of "stoppage of the bowels" in the two years prior to admission. During each of these attacks she had been unable to move the bowels except with strong laxatives; enemas had been unsuccessful. Blood in the stools had been noticed. There had been no loss of weight or appetite. The physical examination revealed tenderness over the colon and a tender, non-movable mass at the junction of the rectosigmoid. Laboratory studies were normal. Roentgenograms revealed an irregular narrowing with partial obstruction of the recto-sigmoid, presumably carcinomatous (figure 11, left). No diverticula were noted. The lesion was resected and found to be a chronic diverticulitis with obstruction.

E. H., a 57 year old male, was first seen in March, 1940, complaining of fatigue, loss of appetite, and epigastric bloating for six months. Roentgen-ray disclosed diverticula and a "saw-tooth" deformity of the lower sigmoid with some narrowing of the lumen (figure 12, top). A low residue, non-laxative diet and antispasmodics were prescribed. The patient progressed very well until June, 1941, when he began to experience pain in the rectum on defecation. The stools were of small caliber, with no blood. Rectal examination disclosed a stony-hard fixed tender mass at the level of the rectosigmoid. Roentgenologically an obstructive deformity was demonstrated in this area with diverticula and evidence suggestive of a walled off perforation. A month later the mass was unchanged and the roentgen-ray deformity looked suspiciously like that of carcinoma (figure 12, bottom). Colostomy was performed in August 1941. The rectal mass decreased slowly in size and finally disappeared although the roentgenologic deformity persisted (figure 13, top). Resection of the lesion in June 1943, proved it to be chronic diverticulitis. The patient has remained well.

B. B., a 56 year old female, complained of weakness, anorexia, and lower abdominal pain for six to eight months. She had not had a bowel movement for seven days prior to admission. During the last two months she had had several gross hemorrhages from the bowel. Physical examination revealed mild abdominal distention; a questionable mass was palpated in the rectum. Laboratory studies disclosed a secondary anemia. Roentgen-ray revealed innumerable diverticula of the colon (figure 13, bottom) with an obstructive lesion of the rectosigmoid. On proctoscopic examination a carcinoma was found as proved by biopsy and by subsequent operation at which time an inoperable tumor was demonstrated.

Diverticula confined to the cecum alone are unusual. Noon and Schenk [43] in 1944, reported three cases of solitary diverticula of the cecum, reviewed the literature and found that up to that time 48 cases had appeared in the American and British literature. The condition was usually diagnosed preoperatively as appendicitis and at the operating table frequently as carcinoma of the cecum. They concluded that minimal surgery should be done because of the tendency of diverticulitis to subside spontaneously. Diverti-

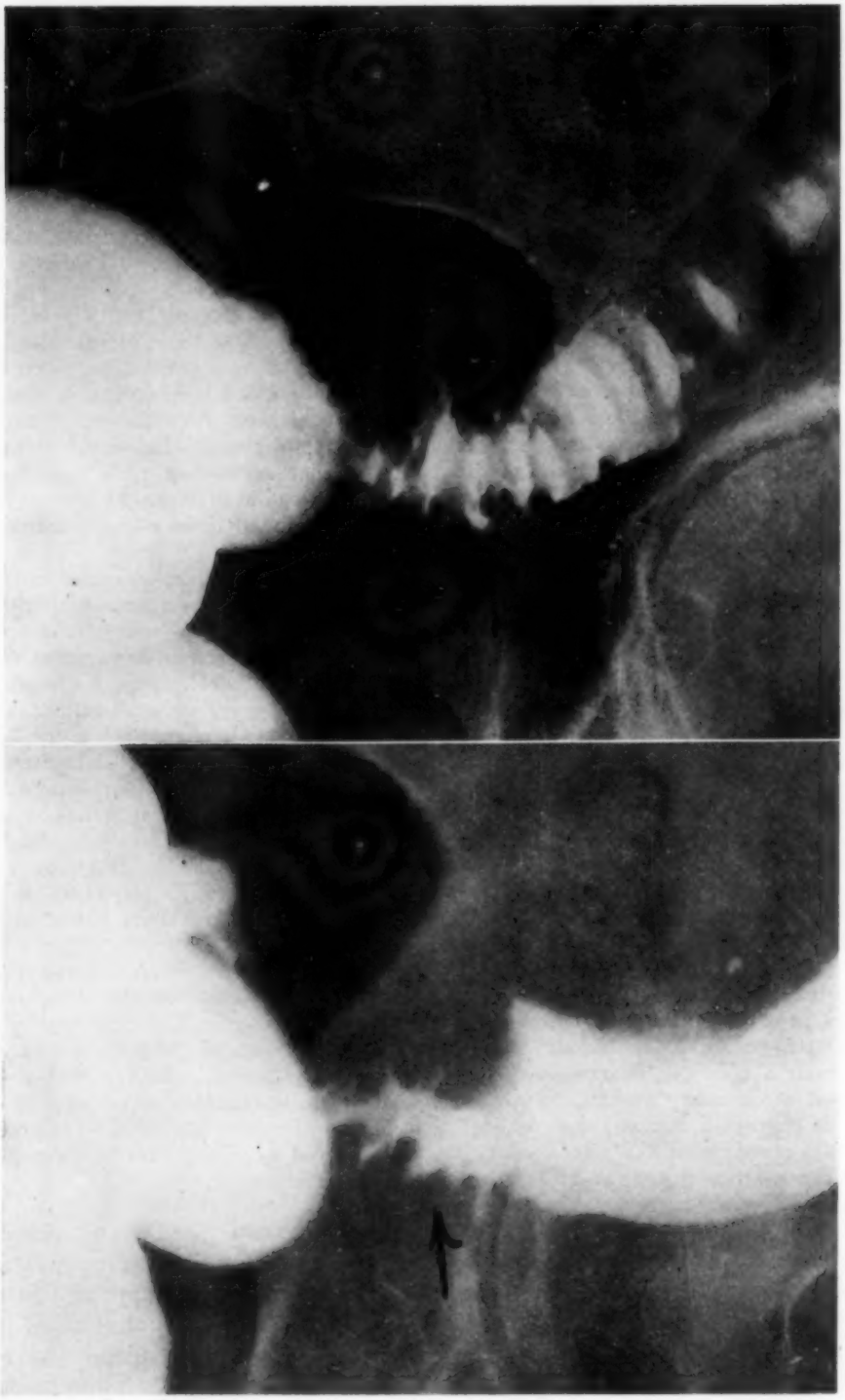


FIG. 12. Chronic diverticulitis of sigmoid with obstruction increasing from March 1940 (top) to August 1941, simulating carcinoma.

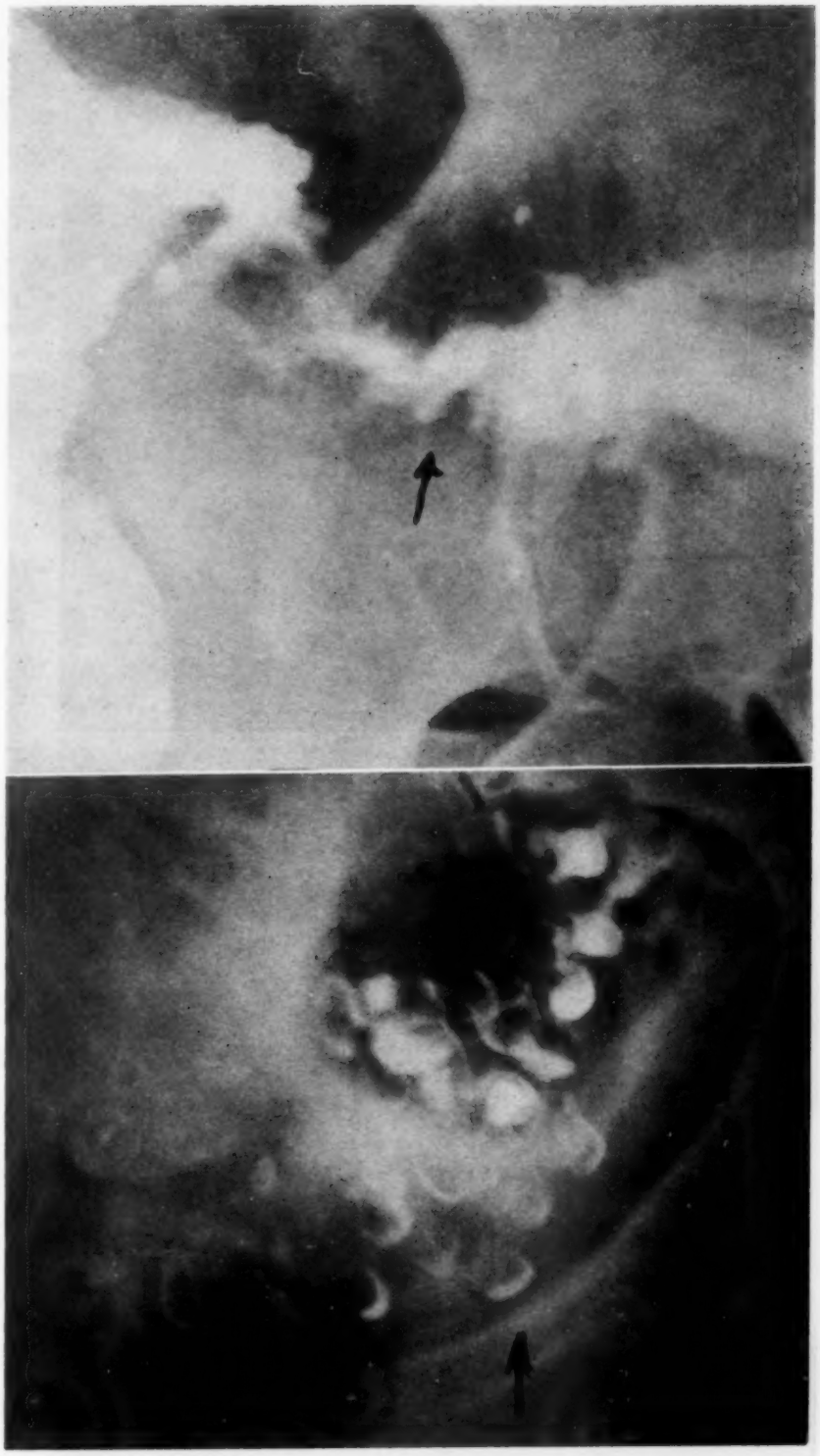


FIG. 13. (top) Persistence of obstructive lesion 21 months after colostomy. (bottom) Extreme diverticulosis of descending colon and sigmoid obscuring carcinoma of recto-sigmoid, demonstrated by roentgen-ray and proctoscopy.

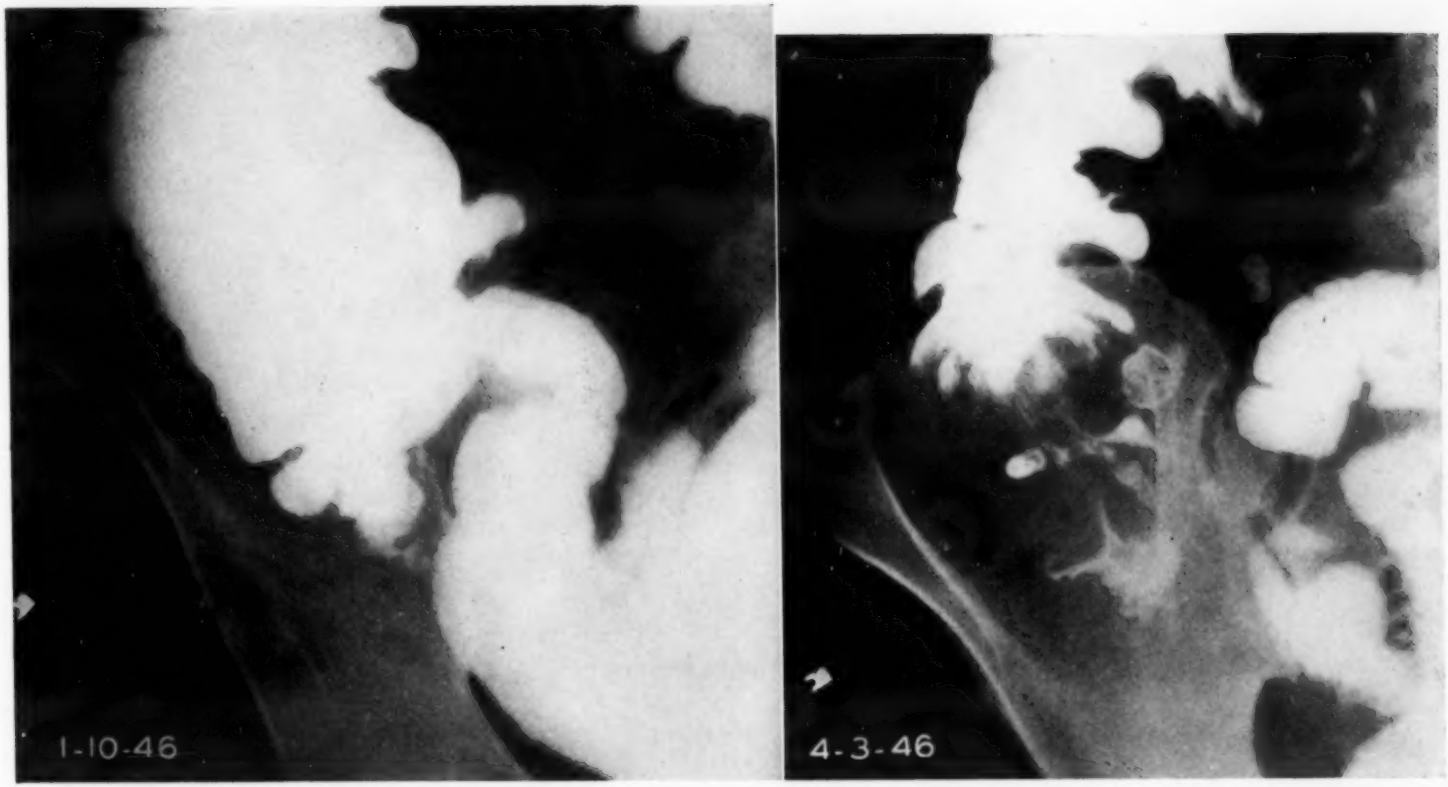


FIG. 14. Diverticulosis of the cecum.

culectomy or inversion of a solitary diverticulum may be indicated in rare instances.[44] The following case is illustrative:

B. M., a 45 year old female, complained of right lower quadrant abdominal distress and gurgling for one month. The distress apparently had no relationship to food; it was relieved by the passage of flatus. Physical examination revealed slight generalized tenderness over abdomen. The laboratory examinations were normal including six stools negative for occult blood by the benzidine test. Roentgen-ray revealed diverticulosis of cecum (figure 14). The patient was reassured; a diet was outlined; antispasmodic drugs were prescribed. Marked improvement has occurred, but the patient still notices some rather localized tenderness and at times discomfort.

Conclusions

Diverticula of the digestive tract, particularly of the colon, are extremely common; the esophagus and duodenum are quite frequently affected; the stomach and jejunum rarely so. Uncomplicated diverticula do not as a rule produce symptoms. An exception is to be found in the pulsion diverticulum of the pharynx in which symptoms may arise early merely from the lodging of food in the "dimple" or in the later stages from the obstruction and kinking of the esophagus produced by the distended sac. Diverticula of the esophagus proper, of the stomach, duodenum and small intestine rarely become inflamed except for the Meckel's diverticula. Diverticulitis of the small bowel simulates acute appendicitis. Diverticula may produce intestinal obstruction from intussusception or from adhesions. Peptic ulcer of Meckel's diverticulum, manifested usually by hemorrhage, is a rather common lesion in children. Diverticulitis of the rectosigmoid ordinarily subsides without surgical interference; in some instances resection is indicated. The differentiation between diverticulitis and carcinoma is at times difficult.

BIBLIOGRAPHY

1. Wallace, R. P.: Traction diverticula of the esophagus, Med. Clin. N. Am., 1942, xxvi, 889–894.
2. Mahle, A. E., and Christopher, Frederick: Esophageal diverticulum, Illinois Med. Jr., 1942, lxxxii, 124–128.
3. Lahey, F. H.: Esophageal diverticula, Arch. Surg., 1940, xli, 1118–1140.
4. Lahey, F. H.: The management of pulsion esophageal diverticulum, Jr. Am. Med. Assoc., 1937, cix, 1414–1419.
5. Lahey, F. H.: Two stage removal of pulsion esophageal diverticulum, Surg. Clin. N. Am., 1939, xix, 591.
6. Moersch, H. J., and Finney, W. S.: Fistula between esophagus and tracheobronchial tree, Med. Clin. N. Am., 1944, xxviii, 1001–1007.
7. Abel, A. L.: Esophageal obstruction, its pathology, diagnosis and treatment, 1929, Humphrey Milford Oxford University Press, p. 69, 102.
8. Reich, N. E.: Diverticula of the stomach, Am. Jr. Digest. Dis., 1941, viii, 70–76.
9. Martin, L.: Gastric diverticula, Ann. Int. Med., 1936, x, 447–465.
10. Reineke, H. G.: Diverticula of upper end of stomach, Am. Jr. Roentgenol., 1941, xlvi, 650–654.

11. Schmidt, H. W., and Walters, W.: Diverticula of the stomach, Am. Jr. Surg., 1941, liii, 315–318.
12. Ogilvie, R. F.: Duodenal diverticula and their complications with particular reference to acute pancreatic necrosis, Brit. Jr. Surg., 1940–41, xxviii, 362–379.
13. Kellogg, E. L.: The duodenum, 1933, Paul B. Hoeber, Inc., New York, page 221.
14. Butler, P. F., and Ritvo, M.: Diverticulum of the duodenum, Boston Med. and Surg. Jr., 1925, cxcii, 705–712.
15. Lahey, F. H.: Surgery of duodenum, New Eng. Jr. Med., 1940, ccxxii, 444–450.
16. Monsarrat, K. W.: Acute perforation of a duodenal diverticulum, Brit. Jr. Surg., 1926–27, xiv, 179.
17. Huddy, G. P. B.: Duodenal diverticula with report of a case of gangrenous diverticulitis Lancet, 1923, ii, 327–330.
18. Lucinian, J. H.: Diverticulum of duodenum perforated into the pancreas, Am. Jr. Roentgenol. and Radium Therapy, 1930, ccxxiv, 684.
19. Beaver, J. L.: Acute perforation of a duodenal diverticulum, Ann. Surg., 1938, cviii, 153–154.
20. Harris, V. C. J.: Diverticulum of the duodenum associated with calculous formation, Brit. Med. Jr., 1932, i, 1080.
21. Finney, J. M. T.: Duodenal diverticula, their significance and treatment, South. Surg., 1942, xi, 543–554.
22. Boland, F. K.: Acute perforated duodenal diverticulum, Surgery, 1939, vi, 65–67.
23. Kozinn, P. J., and Jennings, K. G.: Jejunal diverticulitis, Am. Jr. Dis. Child., 1941, lxii, 620–623.
24. Case, J. T.: Diverticula of the small intestine other than Meckel's diverticulum, Jr. Am. Med. Assoc., 1920, lxxv, 1463–1470.
25. Gerster, J. C. A.: Diverticula of jejunum, Ann. Surg., 1938, cvii, 783–800.
26. Owens, G. H. C.: Acute diverticulitis of jejunum, Brit. Jr. Surg., 1942–43, xxx, 239–240.
27. Bensen, Raymond, Dixon, C. F., and Waugh, J. M.: Non-Meckelian diverticula of jejunum and ileum, Ann. Surg., 1943, cxviii, 377–393.
28. Abraham, Servetnich, and Nichols, H. G.: Hemorrhage from Meckel's diverticulum in an adult, New Eng. Jr. Med., 1943, ccxxviii, 12–14.
29. Abt, J. A., and Strauss, A. A.: Meckel's diverticulum as a cause of intestinal hemorrhage, Jr. Am. Med. Assoc., 1926, lxxxvii, 991–996.
30. Cobb, D. B.: Meckel's diverticulum with peptic ulcer, Ann. Surg., 1936, ciii, 747–768.
31. Mason, J. M., and Graham, G. S.: Ulceration of aberrant gastric mucosa in Meckel's diverticulum, Ann. Surg., 1932, xcvi, 893–910.
32. Matt, J. G., and Timpon, P. J.: Peptic ulcer of Meckel's diverticulum, case report and review of literature, Am. Jr. Surg., 1940, xlvii, 612–622.
33. Abraham, Servetnich, and Nichols, H. G.: Hemorrhage from Meckel's diverticulum in an adult, New Eng. Jr. Med., 1943, ccxxviii, 12–14.
34. Dragstedt, L. R.: Ulcus acidium of Meckel's diverticulum, Jr. Am. Med. Assoc., 1933, ci, 20–22.
35. Nygaard, K. K., and Walters, W.: Malignant tumors of Meckel's diverticulum, Arch. Surg., 1937, xxxv, 1159–1172.
36. Harkins, H. N.: Intussusception due to invaginated Meckel's diverticulum, report of two cases with study of 160 cases collected from literature, Ann. Surg., 1933, xcviii, 1070–1095.
37. Bearse, C.: Diverticulitis and diverticulosis of colon with special reference to patients under 40, Rev. Gastroenterol., 1940, vii, 318–321.
38. Buie, L. A.: Diverticula of the colon, New Eng. Jr. Med., 1939, ccxxi, 593–598.
39. Vital Statistics, Special Reports (Summary of the United States Registration Area, 1936) Dept. of Commerce, Bureau of Census, 1938, iv, 957–958.
40. Mayo, W. J.: Diverticula of the sigmoid, Ann. Surg., 1930, xcii, 739–743.

41. Arnheim, E. E.: Diverticulitis of colon with special reference to surgical complications, Ann. Surg., 1940, cxii, 352–369.
42. Brown, P. W., and Marcley, D. M.: Prognosis of diverticulosis and diverticulitis of colon, Jr. Am. Med. Assoc., 1937, cix, 1328–1333.
43. Noon, Z. B., and Schenk, H. L.: Solitary diverticulitis of the cecum, Am. Jr. Surg., 1945, lxviii, 364–368.
44. Hendtlass, R. F.: Perforated solitary diverticulum of the cecum, Brit. Med. Jr., 1941, ii, 309–310.

FOUR IMPORTANT CONGENITAL CARDIAC CONDITIONS CAUSING CYANOSIS TO BE DIFFERENTIATED FROM THE TETRALOGY OF FALLOT: TRICUSPID ATRESIA, EISENMENGER'S COMPLEX, TRANSPOSITION OF THE GREAT VESSELS, AND A SINGLE VENTRICLE *

By Fred Alexander, M.D.,† and Paul D. White, M.D., F.A.C.P.,‡
Boston, Massachusetts

Today surgery holds much hope for the congenitally cyanotic patient in whom there is a diminution of blood flow to the lungs. Foreknowledge of the existing cardiac condition, of the position of the great vessels, and of any hidden congenital vascular anomaly would favor greatly a successful postoperative result.

Recent surgical advances in the treatment of the Tetralogy of Fallot reflect the importance both of the differential diagnosis and of the careful selection of suitable operative candidates. It is the purpose of this report to present four cases of cyanosis encountered at the Massachusetts General Hospital in which the final diagnosis was at variance with that of the Tetralogy of Fallot. In each of these cases clinical determination of the cardiovascular anomaly preoperatively would have been of great help to the surgeon, who followed in each instance the Blalock procedure, which consists of anastomosing a suitable vessel of the systemic arterial circulation to the pulmonary artery. We shall place special emphasis on a case of the rare tricuspid atresia, because it is coupled with a symptom complex which should differentiate it from other members of its category. In order to facilitate a more complete understanding of the material we are presenting, each case will be followed by a discussion. The four cases include (1) tricuspid atresia, (2) Eisenmenger's complex, (3) transposition of the great vessels, and (4) a single ventricle. Figure 1 illustrates the course of circulation in these four conditions.

Case 1. Tricuspid Atresia.

T. S., a five and one half month old boy of American parentage, was admitted to the Massachusetts General Hospital on July 25, 1945, with the complaint of periodic attacks of persistent cyanosis over an interval of two and one half months. The patient was born at full term by normal delivery; no anesthetic was required. His birth weight was 10 pounds, two and one half ounces. The prenatal course was normal except for maternal vomiting throughout. The infant was bottle-fed from

* Received for publication August 17, 1946.
From the Cardiac Laboratories and Clinics of the Massachusetts General Hospital.
† Cardiac Fellow, Massachusetts General Hospital.
‡ Physician, Massachusetts General Hospital.

birth, many formulas having been tried before a satisfactory combination was found which resulted in a gain in weight. There were no illnesses of any kind until he reached three months of age. His parents then noted that during and after crying spells he presented a coughing type of respiration. During these episodes he would turn blue and become limp and would not regain his normal color until one or more hours later. After having been studied at a local hospital where roentgen-rays revealed the thymus to be enlarged, the child was given a course of deep roentgen-ray therapy in the hope of offsetting these cyanotic periods. However, this was of no avail and the patient was transferred to this hospital for study.

Both father and mother were living and well. One sibling, a four year old brother, had undergone a fusion operation of the spine for tuberculosis.

On physical examination the child's temperature was 99.8, pulse 130, respirations 36, and blood pressure 108 mm. of Hg systolic and 40 mm. diastolic. He was a normally developed, thin infant of a dusky slate blue color, active and aware of his surroundings. The scalp veins were markedly dilated and distended. Examination of eyes, ears, nose, throat, and neck was normal.

Examination of the heart revealed the left border of percussion dullness 1 cm. to the left of the midclavicular line, indicating slight enlargement. The point of maximal impulse was not apparent. Heart sounds were distinct: the rate was rapid and regular. There was a loud (Grade 4) * systolic murmur, best heard in the second and third interspaces just to the left of the midsternal line. No thrill was palpable. P_2 was greater than A_2.

Examination of the abdomen was negative. Reflexes were absent. The extremities showed slight clubbing of the fingers; the entire distal phalanges were blue.

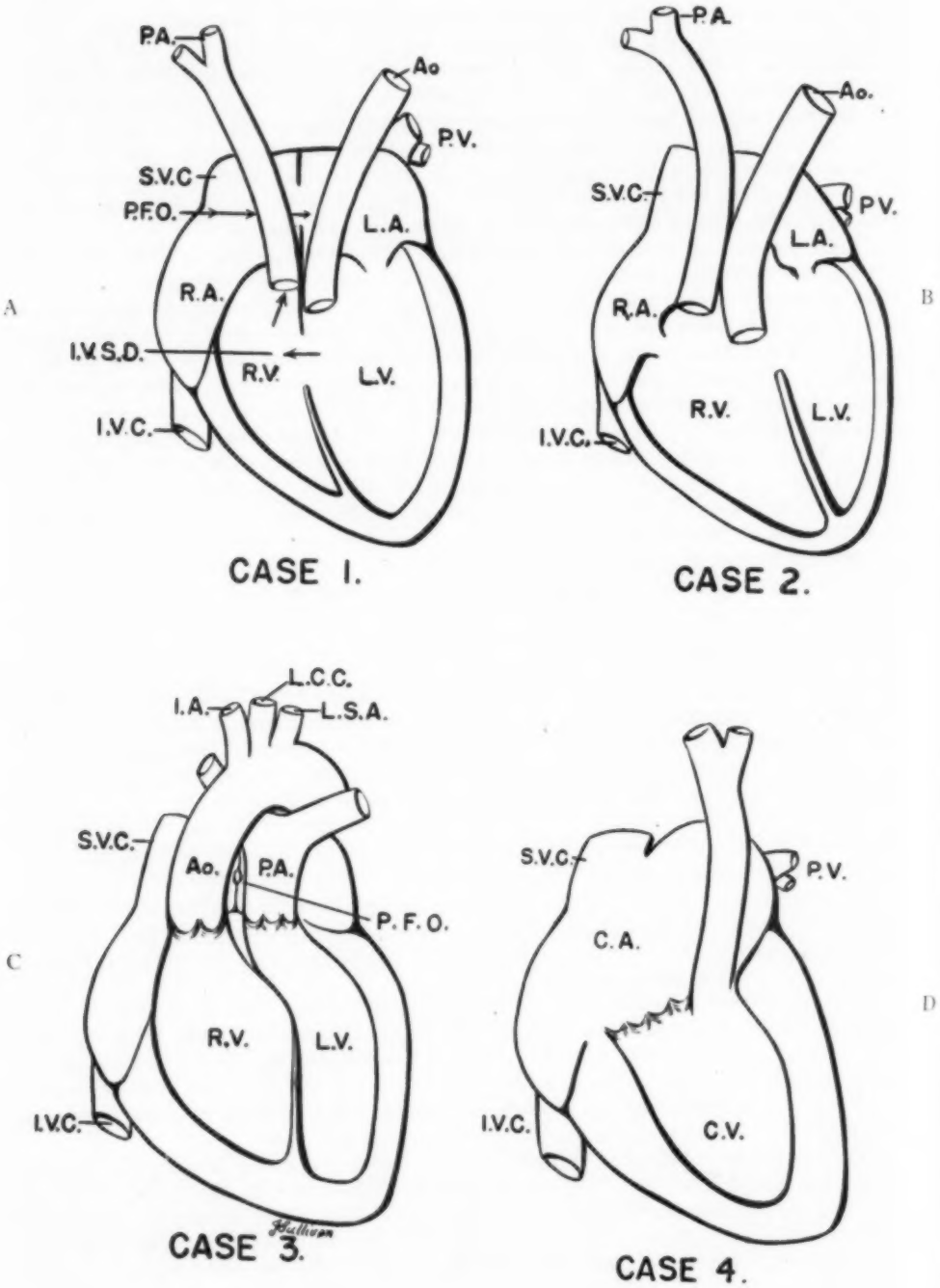
Laboratory studies revealed essentially normal urinalyses except for an occasional blood cell. The red cell count ranged between 7 and 10 million cells per centimeter, and the white blood count ranged between 13 and 14,000 cells per centimeter. Hemoglobin values were between 13 and 16 grams and hematocrit between 40.8 and 73. A Hinton test was negative, as were skin tuberculin test and two blood cultures. The oxygen capacity of arterial blood was 2.7 volumes per cubic centimeter, the oxygen capacity of venous blood 22.6 volumes per cubic centimeter.

Fluoroscopy of the chest revealed the heart enlarged in the region of the left ventricle. There was no evidence of a right-sided aorta. Barium-swallowing function showed no definite abnormality or deformity of the esophagus suggestive of a vascular anomaly. On full roentgen-ray study of the chest the diaphragm was low in position. The costophrenic angles were clear and the lung fields were bright without definite evidence of parenchymal disease. These findings were strongly suggestive of congenital heart disease (figure 2).

An electrocardiogram (figure 3) showed sinus tachycardia at a rate of 150. The P–R interval measured 0.12 second. There was left axis deviation at an angle of $-23°$. The T waves were slightly upright in Lead I, definitely upright in Lead II. The precordial leads were normal, with inversion of T in CF_2 and prominent S waves in $CF_{4,5}$. Subsequent tracings showed no change. The finding of significance in this electrocardiogram is, then, the left axis deviation.

During his hospitalization the patient remained a diagnostic problem as regards the specific cardiac anomaly. He ran an afebrile course with variable respiratory and pulse rates. The number of cyanotic attacks was also variable, sometimes amounting to two or three, sometimes to five or six, a day. These were definitely associated with effort and seemingly were aided very little by oxygen. During these episodes it was noted that the murmur, which was easily audible under ordinary circumstances, disappeared.

* Levine's classification of heart murmurs according to intensity: Grade 1 (faintest murmur audible on most careful auscultation) very slight; Grade 2 slight; Grade 3 moderate; Grade 4 loud; Grade 5 very loud; Grade 6 (loudest murmur one ever hears) loudest.


A
P.A.
Ao
P.V.
S.V.C.
P.F.O.
L.A.
R.A.
I.V.S.D.
R.V.
L.V.
I.V.C.
CASE 1.
B
P.A.
Ao.
S.V.C.
P.V.
L.A.
R.A.
R.V.
L.V.
I.V.C.
CASE 2.
C
L.C.C.
I.A.
L.S.A.
S.V.C.
Ao.
P.A.
P.F.O.
R.V.
L.V.
I.V.C.
CASE 3.
D
S.V.C.
P.V.
C.A.
I.V.C.
C.V.
CASE 4.

On July 30, 1945, digitalis was started because of newly developed dependent edema and increase in the intensity of the murmur. The patient was given 3 mg. of lanatoside-C (Cedilanid) intravenously, followed thereafter by 10 mg. of the powdered digitalis daily. The pulse continued at about 120. During the cyanotic spells the respiratory rate reached 60 to 65 with a slight concomitant rise in the pulse. It was thought that the loud systolic murmur at the basal area and the left axis deviation by electrocardiogram were consistent with the diagnosis of aortic or subaortic stenosis, but the cyanosis and polycythemia pointed to a right to left shunt, such as usually is found in the Tetralogy of Fallot or in a common arterial trunk. At all times the child retained the slate-gray appearance of his skin.

Because no improvement was seen and because corrective surgery in cases of morbus caeruleus has recently been a helpful measure on occasion, the Blalock procedure [15] of anastomosing a sizable branch or tributary of the systemic arterial circulation to the pulmonary artery was thought advisable, the approach in this instance being on the right. The surgical procedure was successful; the right subclavian artery was anastomosed to the pulmonary artery very skilfully.

Postoperatively the child's condition improved, as gauged by a definite decrease in the amount of cyanosis. The respirations, however, continued to be labored and approximately seven and one half hours after the operation the child suddenly took several gasps and died. All supportive forms of therapy in the form of intracardiac adrenalin and coramine were without effect.

Pathological examination at autopsy showed, on superficial examination, a heart globular in shape and enlarged to the left. It weighed 48.5 grams (the normal for this age is 30 grams). The pulmonary artery and the aorta had proper anatomical relationship. The aortic arch arose normally and passed to the left of the trachea and the esophagus. The innominate artery, left carotid and left subclavian arteries also arose normally. The right auricle was normal in size and showed no appreciable hypertrophy. There was no evidence of a tricuspid valve, the orifice site being closed by a smooth, fibrous structure. The left auricle appeared as a cavity formed by the cavernous dilatation of the pulmonary veins, which had fused before approaching the proximity of the heart. The connection between the atria was a defect in the mid-portion of the intra-atrial septum. The mitral valve was seen to consist of one combined valve cusp, together with two small cusps. The left ventricle was dilated. The ventricular wall measured 7 mm. The interventricular septum had a defect

FIG. 1. Diagrams of course of circulation in

A—Tricuspid atresia
B—Eisenmenger's complex

P.A.—pulmonary artery
S.V.C.—superior vena cava
P.F.O.—patent foramen ovale
R.A.—right auricle
I.V.S.D.—interventricular septal defect
I.V.C.—inferior vena cava
R.V.—right ventricle
AO.—aorta
P.V.—pulmonary vein
L.A.—left auricle
L.V.—left ventricle

C—Transposition of the great vessels (complete), and
D—Cor biloculare

I.A.—innominate artery
L.C.C.—left common carotid artery
C.A.—common auricle
C.V.—common ventricle

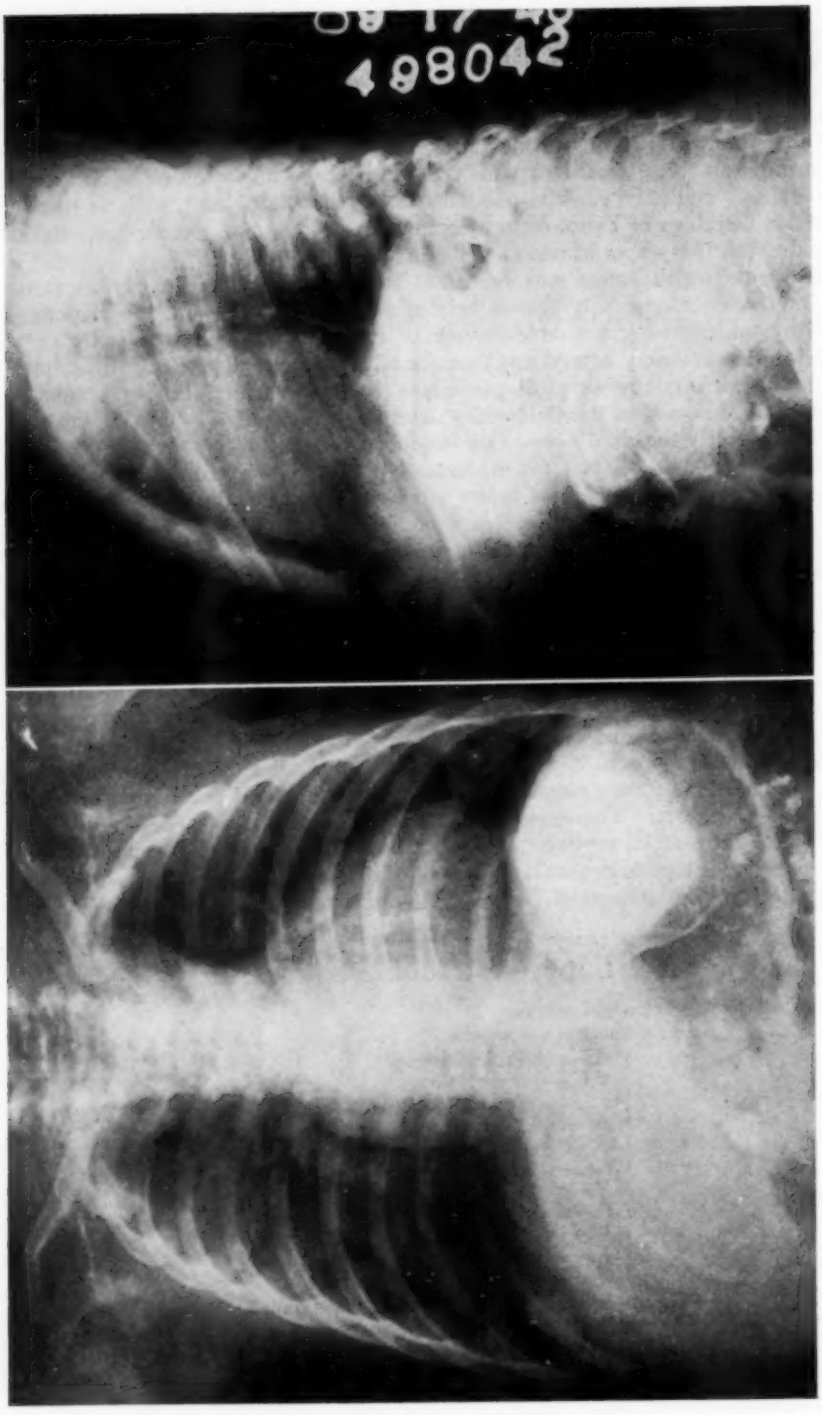


FIG. 2. Roentgenogram of chest in case of tricuspid atresia.

Case 1. A-P View

Case 1. Lateral View

rather high up, which measured 8 mm. in diameter. The aortic valve measured 13 mm., the valve itself being made up of three cusps. The right and the left coronary ostia arose beneath the anterior cusps. The pulmonary valve circumference measured approximately .75 cm. A probe could be passed easily from the left ventricular chamber through the patent interventricular septal defect on into either the aorta or the pulmonary artery. Grossly the remainder of the autopsy was non-contributory.

Of some interest is the finding in the lungs. The right lung had a firm, resilient rubbery consistency. On the lateral surface of the lower lobe there was a friable red blood clot. It had a shaggy surface and was attached to the pleura. The rest of the pleural surface of this lung was blood stained. On section the surfaces of all lobes

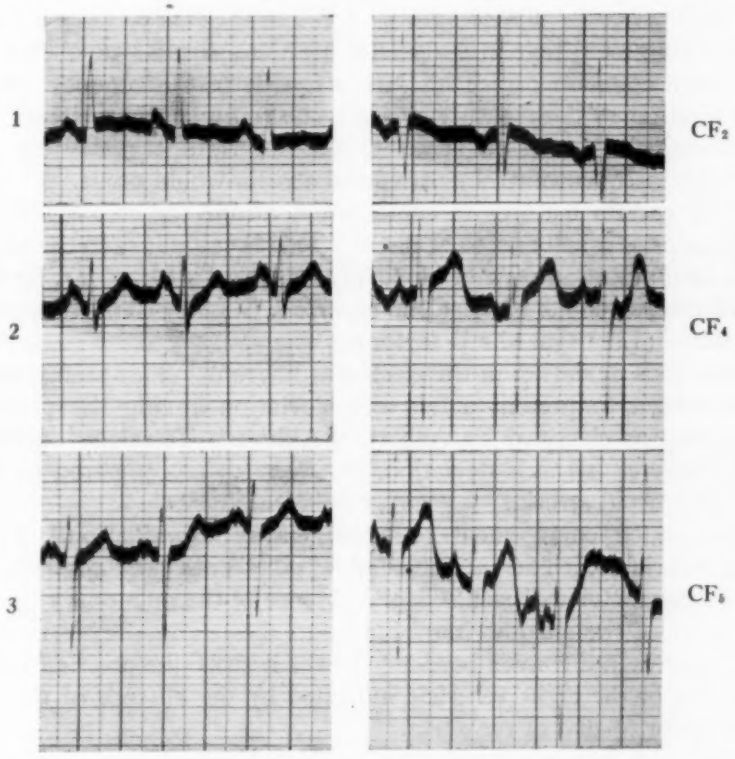


FIG. 3. (*Case 3*) Electrocardiogram in case of tricuspid atresia. Note: Left axis deviation.

were of a dense pinkish-gray, non-aerated appearance almost like that of ground glass. The color and consistency were uniform throughout. The left lung was crepitant and had a pale gray surface. On section it appeared well aerated throughout.

DISCUSSION

Among the infrequently seen and less well recognized entities of congenital heart disease embodied in Maude Abbott's classification of persistent cyanosis[1] is included the combination of tricuspid atresia and right ventricular hypoplasia. A brief review of the literature to date reveals that the total number of cases reported amounts to 34 or more. In the past 10 years

there have been only two examples of this complex in the Massachusetts General Hospital files.

Many theories of origin have been advanced, a few of which may be stated. Rauchfuss [18] believed this to be secondary to an overgrowth and fusion of the endocardial cushions which then obliterate the tricuspid orifice. The endocardial cushions are the anlage of the valve leaflets.

Monckeberg [11] believed that the obliteration of the right a-v orifice results from the unequal division of the primitive atrium by an abnormal shifting of the auricular septum chiefly to the right. This was previously advocated by Vierordt.[17]

Abbott [1] suggested that in early fetal life the auricular canal first opens by means of a common orifice into the left side of the common ventricle. Later, by shifting to the right, it comes to lie more in the midline. However, because it does not shift sufficiently to the right, a maladjustment of the part and consequent mitral or tricuspid atresia would occur.

Clinically certain features in combination afford the clue to diagnosis:

(1) Cyanosis, usually noted at birth. This is secondary to the oxygenation of an insufficient amount of blood (Lundsgaard's L factor), by the admixture of arteriovenous blood (Lundsgaard's C factor) and by peripheral capillary stasis (Lundsgaard's D factor).

(2) Left axis deviation in the electrocardiogram. This seems to be the only type known to present a left axis deviation among the persistently cyanotic group as classified by Abbott.[1] Although Tetralogy of Fallot in dextrocardia gives left axis deviation, P_1 inverted, as compared to the upright P_1 in tricuspid atresia.

(3) Left-sided enlargement on roentgen-ray examination. This has been seen invariably. The cardiac shadow takes on a peculiar outline. In the anteroposterior view, because of the absence of the pulmonary conus, the upper contour of the shadow immediately to the left of the sternum has a concave rather than a convex border. In the left oblique position one notes the small size of the right ventricle indicated by the absence of the cardiac shadow anterior to that of the aorta.

(4) Polycythemia, always present, with clubbing in some instances.

(5) Systolic murmur. A loud systolic murmur, best heard in the second and third interspaces just to the left of the sternal line, has been noted at times in a majority of patients. Taussig [2, 23] believes this to be due to the flow of blood in the patent ductus secondary to the relative pulmonic and systemic pressures. Quite likely an interventricular septal defect also plays a part in its production. Many times the ductus is not patent. Peculiarly, when the child is most cyanotic several investigators have noted the disappearance of the murmur. Apparently tricuspid atresia cannot be ruled out by the absence of this murmur.

(6) Other congenital anomalies. Frequently seen in combination are certain compensatory anomalies, namely, patent ductus arteriosus, inter-

ventricular septal defect, patent foramen ovale, and transposition of the great vessels.

In the case reported here the course of blood could be reconstructed with ease (figure 1 A). Entering the heart via the right auricle, the blood was shunted to the left auricle through the patent foramen ovale. From the left auricle it passed to the left ventricle and then out either into the pulmonary artery and the lungs or into the aorta and the systemic system, access to both being afforded by the patent interventricular septal defect. Pathological study would indicate that the obliteration of the tricuspid orifice occurs about the fourth week and the ventricular septum does not close until the eighth. It has been postulated by Bellett [14] that probably the force of blood flowing from the left to the right ventricle prevents the permanent closure of the septum. Many of these patients do not live beyond one year, although a case has been reported by Hedinger [19] in which the duration of life was 56 years. This span was facilitated by a transposition of the great vessels, which favored the circulation.

Vascular surgery in a child of this age is at best quite a difficult technical procedure. We believe that it has been fairly well established by experience up to the present time that if such a procedure is begun but not completed in a patient as severely incapacitated as are the members of this group it will in most instances prove fatal. It may be advisable to withhold attempts towards correction by surgery until the patient has reached a suitable age, presumably around four or five years of age. The gravity of our patient's situation was accentuated by the child's general debility. This, together with the existence of unsuspected congenital anomalies, led to his untoward end.*

Case 2. Eisenmenger's Complex.

L. C., a five year old boy, was first admitted to the Children's Clinic at the Massachusetts General Hospital in 1943, three years before the present examination, with the chief complaints of shortness of breath and intermittent cyanosis. By history one could not be sure whether he had been cyanotic at birth, which followed a full term, normal pregnancy. At one year he had much difficulty in retaining his feedings, seemed short of breath, and began to have a definite cyanotic tinge to his lips, particularly after playing. From that time to the present he had been followed closely by the clinic physicians. At the age of three years he presented signs of pulmonary congestion but no other signs of congestive heart failure. During this period some retardation of physical growth was noted, together with an increase in the intensity and constancy of the cyanosis. At five years of age the child was brought to the clinic for the purpose of reëvaluation for suitability for the Blalock procedure. The past and family histories were noncontributory. His mother did not have rubella, a rash, or any type of infection during her pregnancy.

On physical examination the child was small for his age. Definite cyanosis of the lips and cheeks, clubbing of the extremities, and mouth-breathing were noted. The tonsils were enlarged but otherwise clear.

* Since this report was written, Dr. Sylvester McGinn has attended a case of a 10 months old baby girl, who proved at autopsy to have the following defects: tricuspid atresia, right ventricular hypoplasia, patent foramen ovale, an interventricular septal defect, and a pulmonary artery which arose in close proximity to the interventricular septal defect.

The heart was enlarged, with the point of maximal intensity in the fifth intercostal space about 6 cm. to the left of the midsternal line (the midclavicular line measured 5 cm.). Heart sounds were heard with relative ease. There was a Grade 2, pulmonary systolic murmur, which was variable with respiration and position change. The blood pressure was 80 mm. systolic and 55 mm. diastolic.

On examination of the abdomen the liver was barely palpable. No edema of the extremities was noted. Laboratory data were as follows: red blood count 7,000,000 cells per cm., white blood count 8,600 cells per cm., hemoglobin 23 grams, hematocrit 55.8, oxygen content (venous) 18.1 volumes per cent, oxygen capacity 25.8 volumes per cent, oxygen saturation 70.2 volumes per cent.

Roentgen-ray (figure 4) revealed extensive enlargement of the heart shadow in the region of the left ventricle and, to a lesser degree, in the region of the left auricle. There was evidence of enlargement of the right ventricle. The hilar vessels were prominent, and there was accentuation of the lung markings throughout both lung fields. The hilar, as well as the pulmonary, vessels showed a definite pulsation. The aorta was small. These findings were consistent with congenital heart disease.

An electrocardiogram (figure 5) showed normal rhythm at a rate of 115, P–R interval equal to 0.15 second, moderate right axis deviation at an angle of 136°, upright $T_{1, 2, 3}$ and inverted T in $CF_{2, 4, 5}$.

During the course of the child's hospitalization the tentative diagnosis of Eisenmenger's complex was made in view of the physical findings, the roentgen-ray film and fluoroscopic evidence of pulmonary congestion, and the right axis deviation by electrocardiogram. He was referred to Dr. Helen Taussig at the Johns Hopkins Hospital, who agreed with this diagnosis. Because of the presence of considerable pulmonary congestion, it was decided that the child was not a fit candidate for the Blalock procedure, which would merely shunt more blood to an already overloaded lung structure. He was digitalized and has been carried along favorably up to the present time.

Discussion

The embryology of the Eisenmenger complex, consisting of dextroposition of the aorta, interventricular septal defect, right ventricular hypertrophy, and a pulmonary artery which is sometimes normal, sometimes dilated, may be discussed briefly at this point. It is the condition of the pulmonary artery which distinguishes this complex from the Tetralogy of Fallot, accompanied as the latter invariably is by a certain degree of pulmonary stenosis.

Rokitansky [24] believed that the Eisenmenger complex was caused by an abnormality in the rotation of the septum bulbi. Spitzer [22] suggested that the complex represents a type of transposition in which the aorta consists of either an incompletely obliterated left aorta or a reopened right ventricular aorta.

Clinically the following factors seem to be rather constant in this complex: (1) There is a definite, distinct prominence of the pulmonary conus with a "dance" of the hilar shadows by fluoroscopy.

(2) The electrocardiogram generally shows right axis deviation.

(3) The systolic murmur may be variable. Some describe it as best heard in the midsternal region, particularly about the third interspace; others, over the entire precordium.

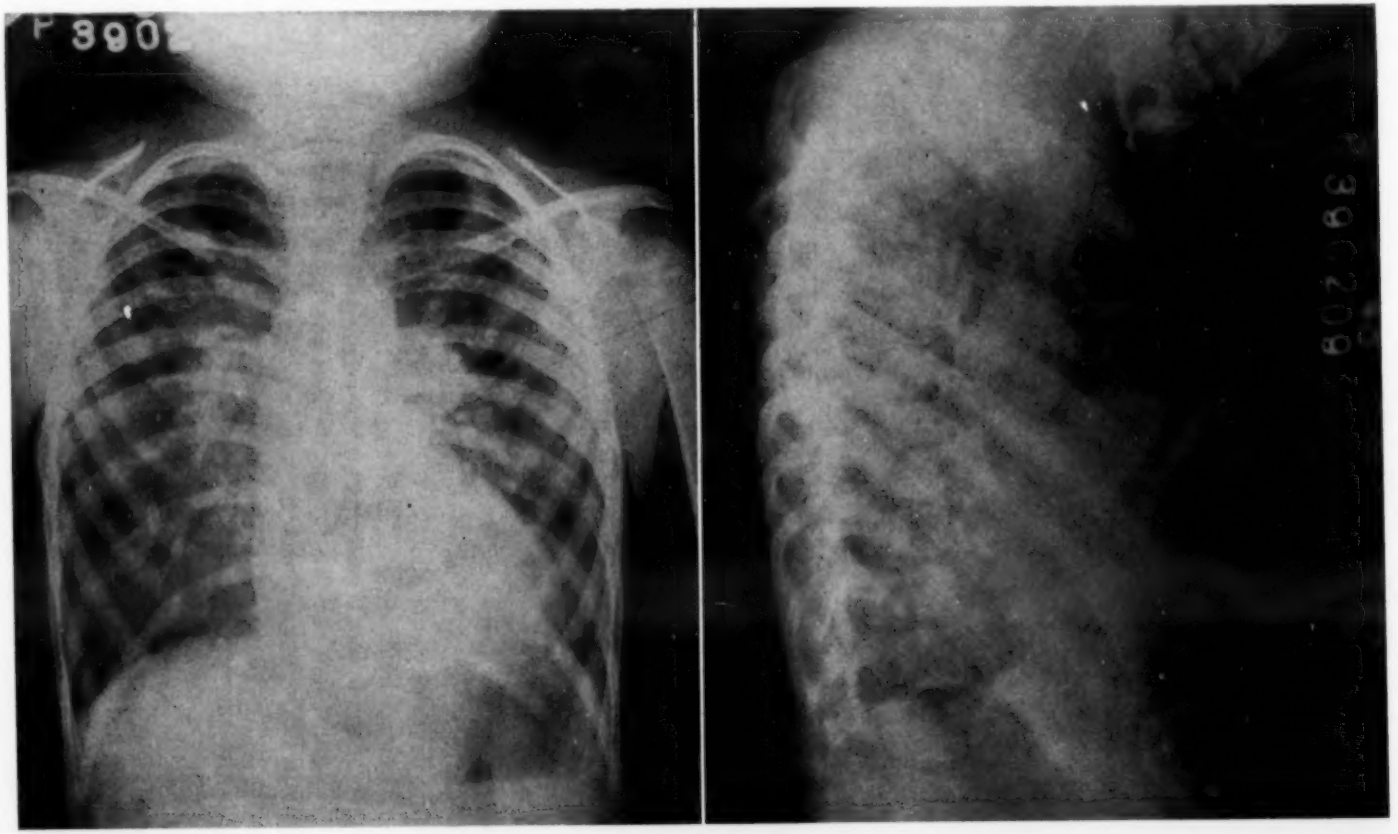


FIG. 4. Roentgenogram of chest in case of Eisenmenger's complex.

Case 2. A–P View

Case 2. Lateral View

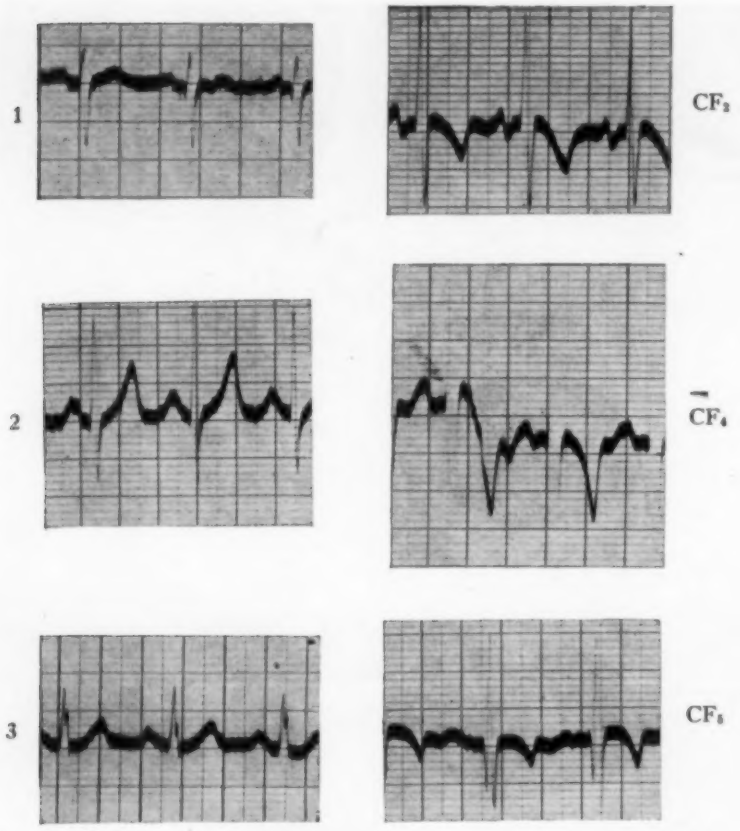


FIG. 5. (*Case 2*) Electrocardiogram in case of Eisenmenger's complex. Note: Right axis deviation.

(4) There seem to be less cyanosis and less clubbing in this complex than in the Tetralogy of Fallot.

(5) At times hoarseness is noted in the Eisenmenger complex because of pressure of the pulmonary conus on the recurrent laryngeal nerve.

(6) Dyspnea may be present, as well as the other, general symptoms of congenital heart disease, such as cough, polycythemia, dysphagia, abnormal susceptibility to infections, weakness, dizziness, convulsions, and tingling of the extremities.

Surgery was avoided in this case, for fear of further burdening of an already overloaded pulmonary circulation. Figure 1 B is a schematic illustration of the heart in the case of Eisenmenger's complex.

Case 3. Transposition of the Great Vessels.

H. G., a 17 year old schoolboy, was admitted to the Massachusetts General Hospital on January 15, 1945, with the complaints of dyspnea and cyanosis. Since birth this boy had been noted to be cyanotic, and for as long as he could remember

he had been short of breath on the slightest exertion. Although there had been no progression of his symptoms during recent years, the existing syndrome had remained apparent, with clubbing of the fingers and toes, marked hoarseness, and periods of epistaxis of short duration and mild intensity. For some time he had not brushed his teeth because of ready bleeding of the gums. Because of the tentative diagnosis of Tetralogy of Fallot, the boy was brought into the hospital for the purpose of determining whether or not he would be a fit candidate for the Blalock procedure.

It may be noted here that the tendency to bleed had increased over the years and that his dyspnea had reached a state where it prevented his playing with other children. Mentally he had found it very difficult to keep up with his school work. The family history was non-contributory, and his mother denied any type of rash or infection during her pregnancy.

On physical examination the patient was severely underdeveloped. Otherwise he appeared well except for marked cyanosis of the face and hands and clubbing of the fingers and toes. There were a moderate number of carious teeth in the mouth. The neck showed prominent arterial pulsations, and there was a noticeable prominence of the left anterior chest.

Examination of the heart revealed it regular and moderate in rate and rhythm. The sounds were well heard. The point of maximal intensity was in the fifth intercostal space, 7 cm. to the left of the midsternal line. There were no murmurs audible at either the apex or base. P_2 seemed prominent. No thrills were felt. The blood pressure was 95 mm. systolic and 55 mm. diastolic.

Laboratory data were as follows: urinalyses essentially normal; red blood count 11,800,000; white blood count 4,800; hemoglobin 164 per cent; hematocrit 86; mean corpuscular hemoglobin 16.6 (29); mean corpuscular hemoglobin volume 36 (34); mean corpuscular volume 46 (85); color index 0.56; arterial CO_2 13.4 m.eq. per liter, 29.6 volumes per cent; arterial O_2 content 16.2 volumes per cent; saturation 62 per cent; checked hematocrit centrifuged three hours at 2360 revolutions per minute, 88.2 per cent. A Hinton test was negative.

Roentgen-ray study (figure 6) showed a heart enlarged in the regions of the left auricle and ventricle. The aorta was small. The hilar blood vessels and the blood vessels throughout the structure of both lung fields were prominent, but no pulsations were seen fluoroscopically. Both lungs seemed emphysematous. The diaphragms were low in position but showed good and equal motion. The superior mediastinum was rather wide, probably due to blood vessel structures. These findings were consistent with congenital heart disease and raised the question of transposition of the great vessels.

An electrocardiogram (figure 7) showed sinus arrhythmia at a rate of 110, P–R interval equal to 0.13 second, marked right axis deviation (angle + 150°) with prominent S–2, upright $T_{1, 2}$, with slight depression of the S–T intervals in these leads, upright T in $CF_{2, 4, 5}$. Of significance, then, in this electrocardiogram was the right axis deviation.

Throughout this boy's hospitalization the diagnosis of Tetralogy of Fallot or some extreme variation thereof was thought most likely by all members of the surgical and cardiovascular departments. Therefore it seemed feasible to offer the patient the expedient of surgery. Before operation the hematocrit level was reduced to 55–60 by repeated small venesections, replacing the blood volume by plasma. Digitalization was carried out because of the cardiac enlargement. On February 2, 1946, the Blalock procedure was attempted, in this case anastomosing the right subclavian artery to the right pulmonary artery, but the operation could not be completed because of the anatomical vascular anomalies unexpectedly encountered. The chest was closed without any definite surgery having been accomplished. Approximately seven and one half hours after operation the patient died.

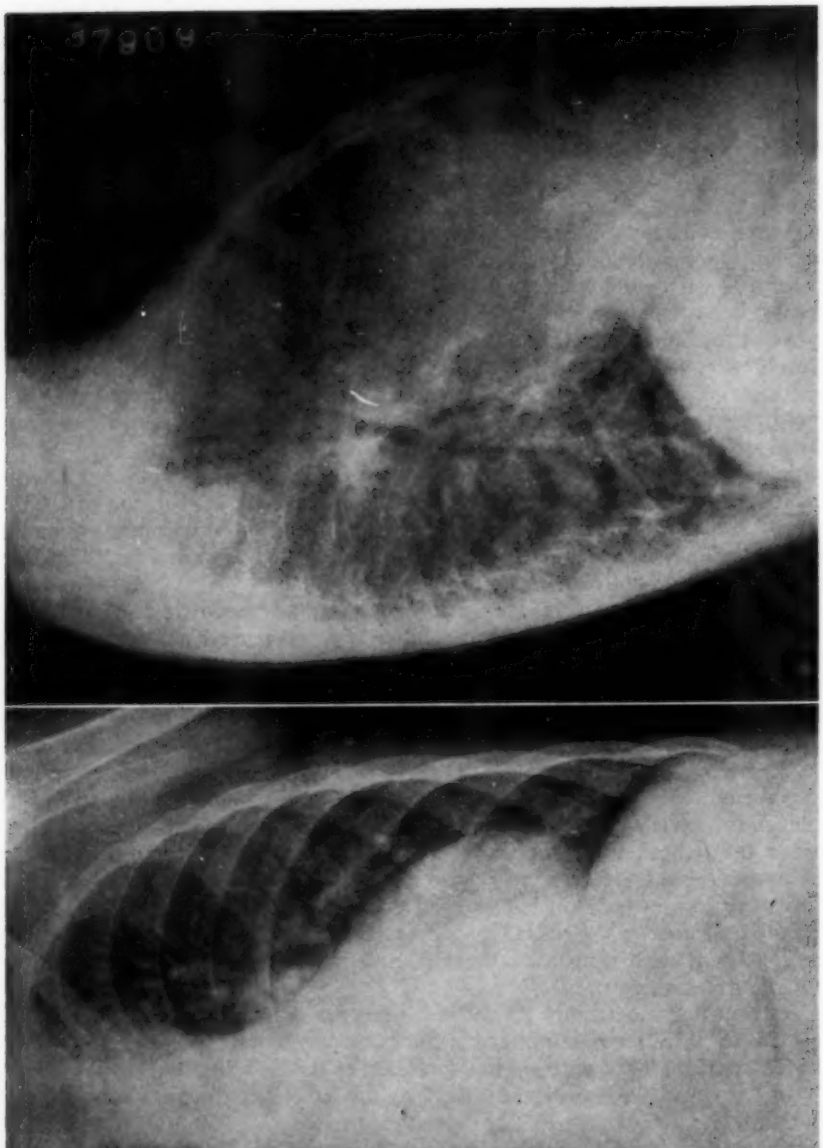


FIG. 6. Roentgenogram of chest in case of transposition of the great vessels (complete).
Case 3. A–P View
Case 3. Lateral View

Postmortem examination revealed the body of a 17 year old boy measuring 135 cm. and weighing approximately 60 pounds but having the appearance of a child of about 10 years of age. There was 4 + clubbing of the fingers and toes. The heart weighed approximately 250 grams. There was a transposition of the origins of aorta and pulmonary artery. The right and left ventricular walls measured 7 mm. Other measurements were as follows: tricuspid ring to the apex 6 cm., mitral valve 7.5 cm., aortic valve 6 cm., tricuspid valve 9.5 cm., and pulmonary valve 6 cm. There were numerous plaques in the pulmonary artery, some calcified. The pulmonary valve was bicuspid. Friable adhesions were present on one of the cusps of this valve. The

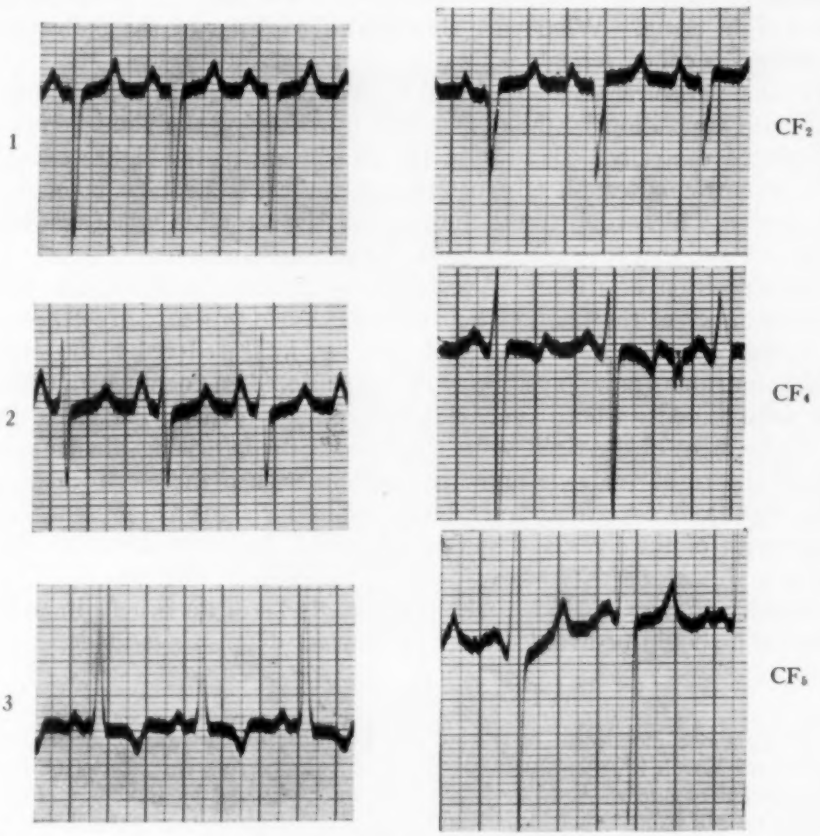


FIG. 7. (*Case 3*) Electrocardiogram in case of transposition of the great vessels (complete). Note: Right axis deviation, prominent S in Leads CF_4 and CF_5.

cavities of the right and the left ventricles appeared to be of about the same size. There was a patent foramen ovale. The coronaries were also patent. Figure 1 C is a schematic representation of the heart in this case of complete transposition of the great vessels.

The trachea and bronchi were filled with clear yellow fluid. The lungs weighed approximately 655 grams. Over the left lower lobe the pleura was ragged because of adhesions. Cut sections revealed edematous lungs which were mildly congested. The right pleural cavity contained about 50 c.c. of dark red blood. The diaphragmatic and visceral pleura were adherent over the left diaphragm. Liver weight was 820 grams; on section this organ appeared to be darker than is usual.

Discussion

Transposition of the great vessels offers a problem in embryology for which many ideas have been postulated. Fundamentally most writers account for the unusual position of the vessels by detorsion of the heart tube in this region and an unwinding of the dextral spiral. Spitzer [22] suggests that the incomplete torsion leads to a fusion of the primary bulbar septum and a reopening of the right reptilian aorta with obliteration of the left. Seemingly, then, the aorta in transposition is not a transposed aorta but a reopened right aorta. What part abnormal absorption of the bulb plays in this process is controversial.

Bremer [20] theorizes that continued growth of the bulb in a dorsal position meets with opposition by the diaphragm, thus forcing the right ventricle to be displaced ventrally. Because of the attachment of the right ventricle to the intraventricular canal, it is suggested that there is a rotary, counterclockwise motion which counteracts the normal dextrotorsion when transmitted to the bulb and that this in turn gives rise to transposition.

Transposition of the great vessels may at least be suspected when a goodly number of the findings listed herewith are present: growth difficulties, cyanosis and dyspnea, spells of fainting, increased red blood count, a variable murmur (apical systolic at times); also when roentgen-ray findings show enlargement of both ventricles, the contour of the right being due to the enlargement of the right ventricle, that on the left being due to enlargement of the right ventricle or both ventricles; when the electrocardiogram shows right axis deviation; and when some minor signs are present, such as enlargement of the liver and spleen, edema of the extremities, or choking cough.

Surgery as it exists today would obviously be of no benefit in this type of case and should be avoided after the correct diagnosis is made.

Case 4. Cor Biloculare.

J. W., a one month old baby boy, was admitted to the Massachusetts General Hospital on March 21, 1946, with the complaint of intermittent attacks of cyanosis over a period of one week. The infant had been delivered by forceps at full term, his birth weight being 5 pounds, 4 ounces. Even though he was not a blue baby at birth, the neonatal course was rather stormy. An oxygen tent was employed for some days because of his difficulty in breathing. While in the hospital he received massage treatment for a deformed left arm. At home he took his formula well and seemed quite content.

About one to two weeks later it was noted that the child turned blue after one of his crying spells. Because these blue spells recurred three to four times each week and the duration increased from three to 30 minutes, the infant was brought to the hospital by his parents. The mother stated that the baby seemed to lose consciousness during the spells. Family history was noncontributory. The mother denied having had a rash or German measles or any type of infection during her first three months of pregnancy. There were no siblings.

On physical examination the child was fairly well developed, although he appeared both dyspneic and cyanotic. His temperature was 99, his pulse 160, and his

respirations were 70. He seemed very restless. The chest was clear to percussion and auscultation except for a few musical râles at the base.

Heart size was slightly increased on physical examination. The rhythm was regular, the rate rapid. Heart tone and quality were fair. There was a Grade 3, systolic murmur at the apex.

Examination of the abdomen revealed the liver edge palpable 3 cm. below the costal margin. The left forearm was slightly deformed, with only four fingers on the left hand. There was a moderate scoliosis.

Complete blood count showed 5,400,000 red blood cells per cu. mm., 7,100 white blood cells per cu. mm., polymorpholymphocytes 70 per cent, lymphocytes 30 per cent. A roentgen-ray film was unobtainable because of the child's grave condition.

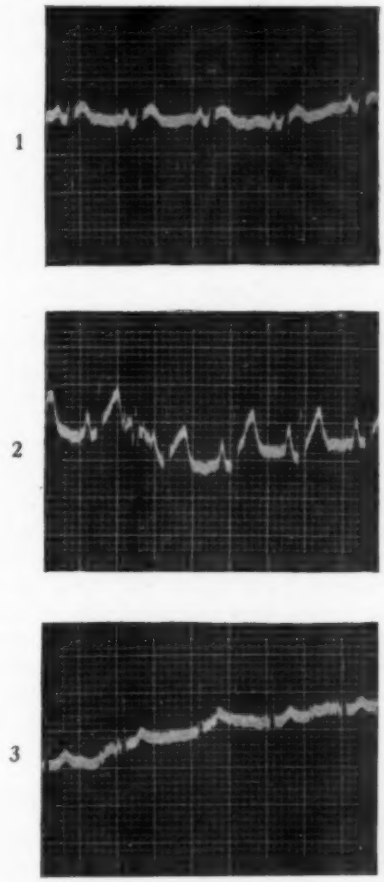


FIG. 8. (*Case 4*) Electrocardiogram in case of cor biloculare. Note: Right axis deviation.

An electrocardiogram (figure 8) showed a sinus tachycardia at a rate of 154, P–R interval equal to 0.08 second, right axis deviation (angle $= +172°$) with prominent S_2, upright $T_{1,2}$ and low upright T_3. The right axis deviation is the finding of significance.

On entry into the hospital the patient was placed in an oxygen tent. Temporarily he seemed much better, his heart sounds improved in quality, and the cyanosis lessened. During the first two days he was digitalized with 0.1 mg. of lanatoside-C (Cedilanid)

intramuscularly, followed by a maintenance dose of 15 mg. of the digitalis leaf. Skimmed milk feedings were accepted. His condition improved during the next two days to such an extent that he was allowed out of the tent for variable periods. Four days after admission the resident was called to see the infant because of a sudden episode of rather intense cyanosis with poor response on stimulation. The pulse was 72; respirations were 120. The baby seemed sluggish, and there was evidence of poor peripheral circulation. Because of his severe dyspnea, oxygen was administered to the child by mask, following which he improved for a while. The râles at the base persisted, as did his murmur, and although his color improved the child remained very ill.

Two and one half hours after this episode he again became deeply cyanotic despite the oxygen and the continued use of stimulants and suddenly cease to breathe. Artificial respiration and the intracardiac use of adrenalin were of no avail. The discharge diagnosis was congenital heart disease, probably a septal defect with resultant respiratory and cardiac failure.

On autopsy the body was that of a malnourished white male infant, measuring approximately 50 cm. in length and weighing 2,500 grams.

The heart was found to lie in a transverse position in the thorax with two vessels 13 mm. in diameter arising from a common ventricular chamber. The anterior vessel divided into branches to supply the pulmonary artery and then continued in the course of the aorta upward, backward, and downward. The posterior vessel passed upward behind the first vessel and branched in the superior mediastinum into the innominate, the left internal carotid, and the left subclavian arteries. It then sent a 6 mm. communicating branch to the other vessels and terminated in the left subclavian artery. There was a single common auricular chamber receiving the venae cavae on the right as well as the right pulmonary veins. The left pulmonary veins emptied into the left side of this chamber. A single four-cusped auriculoventricular valve separated the auricle from the ventricle. The myocardium was firm and averaged 8 to 11 mm. in thickness. The cor biloculare which was thus encountered is schematically shown in figure 1 D.

The lungs were pink and well aerated anteriorly. They were subcrepitant posteriorly and in their dependent portions. Grayish-pink to pinkish-red colorations were seen on section, dark red blood oozing from the cut sections. The liver weighed 86 grams. Its edge measured 3 cm. below the costal margin. On examination the capsule was tense and on section dark red blood was seen to ooze from the cut areas. There were multiple deformities of the skeleton with an absence of the radius and the thumb on the left upper extremity and a marked scoliosis of the spine due to hemivertebrae in the region of T–9 to T–11.

Discussion

Complete cor biloculare is a rare finding, either with division of the truncus arteriosus as here described or without division. One would assume with such an anomaly that there has been arrest in development before the fourth week, that is, before the appearance of the cardiac septa. Clinical recognition of this congenital abnormality as a single entity would appear to be impossible, although there are a few findings which bear mention in this respect. First, there is usually found some degree of cyanosis. Its time of onset is as variable as its intensity, but if the patient lives for a few months at least its presence is always noted. As variable as the cyanosis is the presence of murmurs. Generally there is a systolic murmur heard over

the entire precordium. Usually there is a rather definite degree of right axis deviation by electrocardiogram and an enlarged globular heart by roentgen-ray. Clubbing may or may not be as evident as the other findings consistent with the diagnosis of congenital heart disease.

Obviously surgery would be more detrimental than helpful in a case such as this and in similar cases of more advanced years. As mentioned above, a definite dogmatic diagnosis of such a condition is quite impossible. It may be stated that recently two procedures of diagnostic value, namely angiocardiography and cardiac catheterization with blood gas determinations, have been used to great advantage. The value of the inclusion of these measures in the armamentarium of the diagnostic clinic cannot be overemphasized.

Summary

1. Cases have been presented to illustrate four noteworthy congenital cardiac conditions causing cyanosis which must be differentiated from the more common Tetralogy of Fallot. These four conditions are Tricuspid Atresia, Eisenmenger's Complex, Transposition of the Great Vessels, and A Single Ventricle.

2. Emphasis has been placed in this paper on the case of Tricuspid Atresia and also on its clinical features, which render it a definitely diagnosable entity. The case herewith presented is that of a five and one-half month old boy in whom periodic attacks of cyanosis were noted by the mother and who showed on physical examination a generalized slate-blue color, a Grade 4 systolic murmur in the second and third interspaces just to the left of the midsternal line, and also a palpable liver. By electrocardiogram he presented definite left axis deviation, by roentgen-ray an enlarged heart with no evidence of pulmonary engorgement.

3. A case of probable Eisenmenger's Complex has been described and discussed briefly. This was a five year old boy who complained of intermittent attacks of shortness of breath and cyanosis and on physical examination demonstrated a rather persistent cyanosis, an enlarged heart with a Grade 2, systolic murmur, and a barely palpable liver. Roentgen-ray of the chest showed pulmonary congestion. The electrocardiogram showed right axis deviation.

4. Description of a case of Transposition of the Great Vessels with explanatory notes referable to its embryology and clinical findings was presented. The patient was a 17 year old boy who was said to have been short of breath and cyanotic for the greater part of his life and to have been hoarse and to have manifested some degree of epistaxis only within recent months. Physical examination revealed chiefly a deep cyanosis, clubbing of the digits and toes, an enlarged heart, without murmurs or evidences of pulmonary congestion. Roentgen-ray confirmed the heart size and suggested the possibility of transposition of the great vessels. An electrocardiogram demonstrated right axis deviation.

5. Lastly, a case of A Single Ventricle was described. The child, a one month old boy, was noted to have periodic episodes of cyanosis and also some difficulty in breathing. By physical examination he was moderately dyspneic and cyanotic with an enlarged heart, a Grade 3 systolic murmur at the apex, and a palpable liver. Right axis deviation was prominent in the electrocardiogram.

BIBLIOGRAPHY

1. Abbott, Maude E.: Atlas of congenital heart disease, 1936, Am. Heart Assoc., New York.
2. Taussig, Helen: The clinical and pathological findings in congenital malformations of the heart due to defective development of the right ventricle associated with tricuspid atresia or hypoplasia, Bull. Johns Hopkins Hosp., 1936, lix, 433.
3. Gibson, S., and Clifton, W. M.: Congenital heart disease: a clinical and post mortem study of 105 cases, Am. Jr. Dis. Child., 1938, lv, 761.
4. Harris, J. S., and Farber, S.: Transposition of the great cardiac vessels with special reference to the phylogenic theory of Spitzer, Arch. Path., 1939, xxviii, 427.
5. Walls, E. W.: Biatrial trilocular heart with atresia of the mitral valve, Lancet, 1941, ii, 668.
6. Krumbhaar, E. B.: A congenital cardiac anomaly, Jr. Mt. Sinai Hosp., 1942, viii, 737.
7. Sakaki, J.: Ein Sektionsfall von seltner Herzmissbildung sogenanntes Cor Trilocular Biatrium univentriculare mit der sogenannten kirrirgerten Transposition der grossen Gefässe und der sogenannten Tricuspidalatresie, Mitt. d. med. Gesellsch. zu Tokyo, 1938, lii, 1037.
8. Manhoff, L. J., and Howe, J. S.: Congenital heart disease: tricuspid atresia and mitral atresia associated with transposition of the great vessels, Am. Heart Jr., 1945, xxix, 90.
9. Kuhne, M.: Über zwei Fälle kongenitaler Atresia des Ostium venosum dextrum, Jahrb. f. Kinderh., 1906, lxiii, 235.
10. Bernstein, E. P.: Case of congenital heart disease, Proc. N. Y. Path. Soc., pp. 29, 1906.
11. Monckeberg, J. G.: Die Missbildungen des Herzens *in* Henke, F. and Lubarsh, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, 1924, ii, 1, J. Springer, Berlin.
12. Wieland, E.: Zur Klinic und Morphologie der angeborenen Tricuspidalatresie, Jahrb. f. Kinderh., 1914, lxxix, 320.
13. Rihl, Terplan, Weiss: Über einen Fall von Agenesie der Tricuspidalklappe, Med. Klin., 1929, xxv, 1543.
14. Bellett, S., and Stewart, H.: Atresia of the tricuspid orifice, Am. Jr. Dis. Child., 1927, xlv, 6.
14. Bellett, S., and Stewart, H.: Atresia of the tricuspid orifice, Am. Jr. Dis. Child., 1927, xlv, 6.
15. Blalock, A., and Taussig, H.: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia, Jr. Am. Med. Assoc., 1945, cxxviii, 189.
16. Brown, J. W.: Congenital tricuspid atresia, Arch. Dis. Child., 1936, xi, 275.
17. Vierordt, H.: Primare Fehler am Ostium venosum dextrum, *in* Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, 1901, xv, 2.
18. Rauchfuss, C.: Die angeborenen Entwickelungsfehler und die Fötalkrankheiten des Herzens und der grossen Gefässen *in* Gerhardt's Handbuch der Kinderkrankheiten, 1878, iv, 99, H. Laupp, Tübingen.
19. Hedinger, E.: Transposition der grossen Gefässe bei rudimentaren linker Herzkammer bei in 56 jahrigen Frau, Centralbl. f. allg. Path. u. path. Anat., 1915, xxvi, 529.

20. BREMER, J. L.: Transposition of the great vessels, Arch. Path., 1942, xxxiv, 1016.
21. SAPIR and LEV: Tetralogy of Eisenmenger, Am. Heart Jr., 1945, ii, 3.
22. SPITZER, A.: Über den Bauplan des normalen und missbildeten Herzens, Virchow's Arch. f. path. Anat., 1923, ccxliii, 81.
23. TAUSSIG, H.: Clinical and pathological findings in congenital malformation of the heart due to defective development of right ventricle associated with tricuspid atresia or hypoplasia, Bull. Johns Hopkins Hosp., 1936, lix, 435.
24. VON ROKITANSKY: Die Defecte der Scheidewände des Herzens. Pathologishanatomische Abhandlung VI (21): 156, pp. 11, fol. Wien, W. Braumüller, 1875.

NEPHROGENIC DIABETES INSIPIDUS: TRANSMITTED BY FEMALES AND APPEARING DURING INFANCY IN MALES *

By Robert H. Williams, M.D., and Cole Henry, M.D.,
Boston, Massachusetts

This paper reports an unusual type of diabetes insipidus. This entity has most likely existed before, but we have not found any evidence of its recognition as such. Before discussing the characteristics of the syndrome, a presentation of our studies is given, chiefly in the order that they were conducted.

Patient C. H. A physician, aged 35, was recently admitted to the Boston City Hospital with pneumonia. His past health had been good, but he stated that he had had diabetes insipidus since infancy. In the course of treating the pneumonia with sulfadiazine it was observed that the concentration of this compound in the blood was unusually high in spite of a daily urine volume of about 12 liters. This observation and the fact that several members of the family had had diabetes insipidus since childhood aroused special interest.

This patient, like six others in five generations of his family, was told that he was a "water baby." When he was one month of age, or younger, his parents noticed that he desired excessive amounts of fluid and that he had a large urine volume. In spite of the persistence of these symptoms, his growth and development proceeded fairly well. However, he never appeared to be very strong and he did not grow to be as large as the average individual, although he had good stamina. His appetite has not been very remarkable, but he never has had much desire for sweets or salt. He has had a great desire for fruit and he has used black pepper freely. He likes meat moderately well.

He has known for eight years that he had hypertension, the systolic blood pressure ranging from 130 to 140 mm. of mercury and the diastolic pressure from 90 to 95. During this time his urine has been examined many times, but it has never been found to contain albumin, sugar or formed elements. The daily urine volume has been determined occasionally and it has been found to vary from 8 to 24 liters per day, with a specific gravity of about 1.001. The ingestion of sodium chloride caused a moderate increase in thirst. On two occasions water was denied for about seven hours and the patient developed a circulatory collapse each time. In 1940 he was given, intramuscularly, 1 c.c. of pitressin tannate in oil every two days for eight days, but this treatment caused no decrease in the urine volume. Large doses of sodium bicarbonate caused a slight decrease in the amount of urine excreted.

He occasionally has had headaches, but these do not tend to be severe. There have been no visual complaints, sensitivity to cold, brittleness of hair or nails, drowsiness nor gonadal disturbances. A careful systemic review elicited no additional complaints.

On physical examination the patient was found to be smaller than average. His weight was 120 pounds and his height was 5 feet and 6 inches. He appeared

* Received for publication November 18, 1946.
From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, the Department of Medicine, Harvard Medical School, and the Mallory Institute of Pathology, Boston City Hospital, Boston, Massachusetts.

somewhat older than his age of 35 years. The skin was quite unusual in texture and appearance, being pale, shiny, scaly, very dry, coarse, inelastic and parchment-like. The epidermal layer was distinctly thickened. Systolic blood pressure varied from 130 to 175 and the diastolic pressure ranged from 80 to 125. The fundi, thyroid, heart, lungs, abdomen, sexual hair, gonads and neurological examination appeared to be normal.

The urine was pale and the specific gravity was 1.001–1.002. It contained no albumin, sugar, or formed elements. The hemoglobin varied from 82 to 95 per cent of normal. The red blood cell count was 4,300,000 and the volume of packed red blood cells was 42 per cent. Four estimations of the non-protein nitrogen of the blood yielded normal values. The carbon dioxide combining power of the plasma was 42 volume per cent on two occasions. Estimations of creatinine yielded 1.1 and 1.2 mg. per 100 c.c. of blood. The concentration in the serum of sodium, potassium and chloride was normal or slightly elevated (table 1).

TABLE I

Electrolytes in Serum

Date	Sodium, m.eq./l.*	Potassium, m.eq./l.*	Chloride, m.eq./l.*
6/20	139.9	4.3	113
6/20	140.0	4.2	108.5
11/24	136.5	4.6	102.2
11/26	142.2		110.5
11/28	146.0	5.0	115.0

* All of the specimens were taken while the patient was in a fasting state, but the amount of water previously ingested varied.

The basal metabolic rate was plus 26 per cent of normal. With the patient in a fasting state there were 120 mg. of glucose per 100 c.c. of blood. After the administration of 75 gm. of glucose, orally, the blood glucose concentration after 30, 60, and 120 minutes was 170, 210, and 180 mg. per 100 c.c., respectively. Another test was conducted, administering 75 gm. of glucose, orally, and 0.1 unit of insulin per kilogram of body weight, intravenously. There were 100 mg. of glucose per 100 c.c. of blood before this treatment was given and after 60, 120, and 220 minutes were 140, 120, and 100 mg., respectively. No sugar appeared in the urine. These tests can be interpreted as indicating the existence of diabetes mellitus with possibly slight insulin resistance. There were 8.9 mg. of 17-ketosteroids excreted in the urine per 24 hours. Roentgenograms of the skull, lumbar vertebrae, pelvis, chest, and abdomen revealed no abnormalities.

The average daily excretion of urine during an interval of 17 days was 10,600 c.c. Several compounds were administered, consecutively, in an effort to modify the volume of urine. The quantity of the latter was determined at frequent intervals throughout the day in order to detect any brief effect that might be exerted. Twenty mg. of desoxycorticosterone acetate in oil when injected, intramuscularly, had no effect. Ten c.c. of adrenal cortical extract was without effect. Potassium chloride, given in doses of 2 gm. six times daily, caused a slight decrease in thirst and in the urine volume.

When 1 c.c. of pitressin tannate in oil was given, intramuscularly, no definite decrease in urine volume resulted, but within 30 minutes after the

injection the patient had a slight chill and a rise in his temperature to 101° F. A few days subsequently he was given 0.1 c.c. of pitressin, intradermally, in the forearm. Within 30 minutes a violent local reaction had developed. At the site of injection there was a firm, white wheal, about 10 by 6 cm. Extending towards the shoulder was an edematous streak which was about 15 cm. long. The reaction was soon inhibited by the injection of 15 c.c. of saline containing ½ c.c. of 1 : 1,000 dilution of adrenalin.

The marked allergic reaction to pitressin was considered as possibly accounting for the absence of its antidiuretic effect. In order to test the antidiuretic effect of large doses of pitressin, the patient was desensitized to to this solution. Beginning with 0.1 unit of pitressin and progressively increasing the dosage, 17 injections of this drug were given within 30 hours. At the end of this time no local or general allergic reaction to pitressin resulted, even in doses of 1 c.c. (20 pressor units), but there was only a very slight, if any, antidiuretic effect. The phenomenon was regarded as possibly analogous to that observed in three patients with diabetes mellitus, seen by one of us (R. H. W.), who had local inflammatory reactions to insulin and showed no response in the blood sugar to injections of more than 100 units of insulin.

The question for consideration was whether antibodies had been produced which were capable of destroying the pitressin. Studies were conducted with rats to test this hypothesis.

To 0.9 c.c. of the patient's serum was added 0.1 c.c. of pitressin and the mixture, after sitting at room temperature for one hour, was injected, intravenously, into rats. The antidiuretic effect of this solution was tested by the method of Ham and Landis.[1] The control solutions for the experiment consisted of: (*a*) 0.9 c.c. of serum from a normal man plus 0.1 c.c. of pitressin (2 pressor units), (*b*) 1 c.c. of normal serum, (*c*) 1 c.c. of patient's serum, (*d*) 0.9 c.c. of saline and 0.1 c.c. of pitressin, and (*e*) 1 c.c. of saline. Each of these solutions was given intravenously to a group of three male rats, each weighing approximately 300 gm. The animals given sera with pitressin added excreted 25 per cent less urine than those given any of the other solutions. Therefore, it was concluded that under the conditions of the experiment the serum did not inactivate the pitressin.

The next question was whether pitressin was inactivated in the patient's body at an abnormally rapid rate. To test this possibility 1 c.c. of pitressin was administered subcutaneously to the patient and a similar injection was given to a normal individual. Thirty minutes later blood was withdrawn and a few minutes thereafter 2 c.c. of serum was injected intraperitoneally into rats. The urine flow was then followed for the next three hours. The serum from the untreated normal subject had no antidiuretic effect whereas the sera of the subjects injected with pitressin had a marked antidiuretic effect.

After giving the patient as much as 3 c.c. of pitressin (60 pressor units)

within six hours, no more than a very slight antidiuretic effect was observed. The above experiments with the rats had indicated that inactivation did not seem to take place abnormally rapidly. Furthermore, after the injection of 0.5 c.c. or more of pitressin, there was generalized blanching of the skin and abdominal cramps, as well as an increase in the blood pressure. Therefore, it was evident that the pitressin was exerting several of its systemic effects, but was failing to affect the reabsorption of water by the kidneys.

These observations suggested that there might be an anatomical, or at least a physiological, defect in a specific segment of the renal tubules. At this point the possibility that there was an even greater production of posterior pituitary principle was considered, since it was believed that the patient often was in a state of dehydration, which Gilman and Goodman [2] found usually leads to an increased availability of the antidiuretic hormone. Moreover, the patient's pallor and hypertension might possibly have been related to increased function of the posterior pituitary lobe. His serum was given to rats, intravenously, in doses of 1 c.c. and its antidiuretic effect was tested in the manner described above. Control specimens of serum were taken from two normal individuals. Another sample of serum was obtained from a normal subject who had drunk 7,000 c.c. of water during the 24 hours previously. Saline was injected into other animals to serve as additional controls. However, no antidiuretic effect was found to be exerted by the serum of any of the subjects.

A series of tests was conducted to establish the extent and site of impairment of renal function. The patient and a normal individual who was essentially the same size were compared in their capacity to excrete sodium chloride. The control subject had a normal blood pressure and phenolsulphonphthalein excretion; routine examination of the urine revealed no abnormalities. Each individual was in a fasting state and had had no water for one hour. The subjects were asked to void and this specimen was discarded, but hourly collections of urine were made during the next four hours. No treatment was given during the first hour, but throughout the next 45 minutes an intravenous infusion of 1,500 c.c. of normal saline was given at a fairly constant rate. Specimens of blood were taken at hourly intervals. Estimations were made of the sodium and chloride in the blood and urine (table 2). During the one hour control interval each subject excreted about the same amount of sodium and chloride, although the patient excreted more than twice as much urine as did the normal subject. During the hour following the beginning of the saline infusion the patient excreted distinctly less of these electrolytes than did the normal individual, but during each of the subsequent two hours the reverse was found. Throughout the entire four hours the patient excreted about 32 per cent more sodium and chloride than did the normal individual, yet the urine volume was about 300 per cent greater. The chloride concentration of the serum increased markedly in the patient, but it did not show any significant change in the normal subject.

TABLE II

Rate of Excretion of Sodium and Chloride
(After the infusion intravenously of 1,500 c.c. of normal saline)

Subject	Hourly Intervals	Urine					Serum	
		Volume, c.c.	Sodium		Chloride		Sodium, m.eq./l.	Chloride, m.eq./l.
			m.eq./l.	total m.eq.	m.eq./l.	total m.eq.		
Normal	Control	150	20.4	3.1	41.8	6.3	140	110
	1	135	96.2	13.0	111.2	15.1	138.5	108.9
	2	145	66.4	9.7	85.0	12.3	141	107
	3	142	101.9	14.5	132.1	18.7	—	—
Patient C. H.	Control	380	6.9	2.62	16.7	6.3	142	106.2
	1	480	12.1	5.8	23	11.0	140	118.5
	2	810	25.8	20.9	30.3	24.5	143	122
	3	680	35	23.8	40.3	27.4	140.8	117.5

During the course of this test the individual with diabetes insipidus became pale, weak and intensely thirsty. He also had a slight drop in his blood pressure.

Following the injection, intravenously, of 1 c.c. of phenolsulphonphthalein, there was found: none in the urine within 15 minutes, 5 per cent after 30 minutes, 15 per cent after 60 minutes, and 20 per cent after 120 minutes. There was also impairment in the clearance of the blood of urea and of creatinine from the plasma (table 3). Despite the marked diuresis, sodium and potassium were eliminated from the body less rapidly than normal, probably indicating increased tubular reabsorption of these elements. In three patients with diabetes insipidus of the "pituitary type," studied by

TABLE III

Renal Clearance of Blood and Plasma

Subject	Urine, c.c./min.	Clearance, c.c./min.				
		Blood	Plasma			
		Urea	Creatinine	Sodium	Potassium	Chloride
Normal	1	75	175	3.0	20	
Patient C. H.* Test No. 1	6.3 (630%)	29.8 (39.7%)	105 (60%)	0.312 (10.4%)	4.54 (22.7%)	0.932
Test No. 2	7.0 (700%)	35.4 (47.1%)	99 (57%)	0.379 (12.6%)	8.85 (44.2%)	1.24
Diabetes Insipidus (Pituitary)				3.2	21	

* Patient in a fasting state; no fluid during test and none for 2 hours before it.

Dr. John Talbott at the Massachusetts General Hospital, the sodium and potassium clearances were found to be normal.[3]

Special studies of renal function [4] were conducted to determine the chief site of impairment.* The renal plasma flow was measured by the diodrast clearance and the glomerular filtration by the mannitol clearance. Diodrast and glucose were used to study, respectively, the maximal excretory and reabsorptive capacities of the tubules. There was shown to be a decrease in renal plasma flow without much change in glomerular filtration (table 4).

TABLE IV

Special Renal Function Studies

	Normal	Patient C. H.	Diabetes Insipidus (Pituitary)*
Renal Plasma Flow, c.c./min.	697 (±136)	450	480
Glomerular Filtration, c.c./min.	130 (±20)	106	113
Filtration Fraction, %	19 (±2)	23.6	26
Diodrast Tm, mg./min.	52 (±9)	27.7	43
Glucose Tm, mg./min.	375 (±79)	417.3	—

* These data are taken from Winer.[5]

The resulting increase in the glomerular filtration fraction may imply that efferent arteriolar constriction exists. The maximal rate of glucose reabsorption (glucose Tm) was normal, while maximal tubular diodrast excretion (diodrast Tm) was reduced by about 50 per cent. These changes in renal function are similar to those found in diabetes insipidus of the "pituitary type," and are consistent with the pattern found in essential hypertension. Dissociation between glucose and diodrast Tm is frequently seen in the course of hypertensive disease, but not of the magnitude seen in this case. The marked impairment in the secretion of diodrast and phenolsulphonphthalein is apparently due to impairment of active tubular excretion, but the normal glucose Tm indicates a normal mass of functioning proximal tubular tissue. This interpretation would explain the defect in water reabsorption which has led to continuous polyuria in this patient. In the course of the special studies the urine flow was observed to be between 14 and 28 c.c. per minute, which is about four times the volume in normal individuals under the same circumstances.

After making the foregoing observations an effort was made to study six other members of the family affected with diabetes insipidus. It was not

* The authors are very grateful to Dr. Stanley Bradley of the Evans Memorial Hospital, Boston, who very kindly performed these tests and aided in interpreting the results.

possible to examine any of these patients, but some information, given below, was obtained from hospital records, from the patients or from their relatives.

Patient M. R. A clerk, aged 53, has been admitted to a veterans' hospital in Tuscaloosa, Alabama, on six occasions during the past 12 years. We are grateful to Dr. Dave Robertson for submitting to us the pertinent information that has been accumulated in this case. The patient stated that he had drunk an excessive amount of water since birth. The volume of his urine has been estimated many times and was found to average about 18 liters per day. He grew fairly well, but he has always been somewhat shorter than the average individual. He has had hyperorexia for many years, apparently eating a balanced diet with an average amount of salt. Occasionally he has severe diffuse headaches and feels dizzy and weak. The accumulated diagnoses are: diabetes insipidus, hypertrophic arthritis, blindness of right eye, corneal scar on the left eye, chronic otitis media, myocardial disease, complete atrophy of the right testicle, and chronic prostatitis. His height is 68 inches and he weighs 193 pounds. The hemoglobin determinations and the red blood cell counts were normal repeatedly. The examination of many specimens of urine revealed a specific gravity which varied from 1.000 to 1.003 and usually a neutral reaction. Albumin was sometimes present in small amounts and at other times none was found. Occasionally many white blood cells were present, but usually there were no formed elements in the urine. No glycosuria was ever found, but six fasting blood sugar estimations yielded values ranging from 105 to 147 mg. per 100 c.c. The concentrations in the blood of non-protein nitrogen, creatinine and urea nitrogen were normal. Eighty-five per cent of phenolsulphonphthalein injected intravenously was excreted in the urine within two hours. Two dilution and concentration (Mosenthal) tests revealed a maximal range in specific gravity of from 1.000 to 1.005. During these tests the patient developed circulatory collapse as a result of dehydration, and during one of them he became unconscious. Although he excreted only 724 c.c. of urine during one interval of 12 hours and 755 c.c. during another such period, the maximal specific gravity was 1.006.

Roentgenograms of the skull showed slight calcification in the region of the pineal body and the sella turcica was normal.

He was given 1 c.c. of pituitrin daily for four days, but there was no antidiuresis. However, he developed a marked febrile reaction following the last injection.

During the last 11 years his blood pressure has gradually risen from 115 to 160 systolic and from 84 to 106 diastolic.

Patient R. L. A veteran of the Army Air Force, aged 33, has been hospitalized for most of the past year with a urinary tract infection.

During the first month or two after birth it was observed that he drank an excessive amount of fluid and he urinated frequently. After a few years his symptoms largely disappeared, but he continued to drink as much as four quarts of water per day and got out of bed from one to three times per night to urinate.

His growth and development were normal. He had several examinations on entering the Air Force, but apparently no abnormalities were found. About one year ago he received an injury in the region of the left kidney on landing with a parachute. Since then he has not felt well. He was found to have dilation of his ureters and a urinary tract infection, which has not responded satisfactorily to prolonged treatment with penicillin and sulfonamides. The non-protein nitrogen has remained at about 70 to 100 mg. per 100 c.c. of blood. He has never received pituitrin therapy.

Patient W. M. A boy, 17 months of age, was apparently normal at birth. By the end of two months he stopped gaining weight, so breast feedings were discontinued and a formula was given. He became fretful and varied a great deal in his desires

for milk and water. At four months he developed a fever which rose to 107° within a few days. He was then taken to the University of Virginia Hospital, where many studies were conducted, a report of which was kindly supplied to us by Dr. William Waddell. Numerous urine examinations were made, but at no time was there any albumin, sugar, or cellular elements. The specific gravity varied from 1.006 to 1.010. The blood ureas were 45 and 37 mg. per 100 c.c. Numerous blood cultures were negative. The blood chloride was 655 mg. per 100 c.c.

In view of the uncertainty of the diagnosis, an exploratory operation was performed, but nothing remarkable was found; the kidneys seemed normal grossly. Two pyelograms, made after intravenous injection of the opaque medium, revealed normal appearing kidneys.

The amount of fluid ingested and excreted was not abnormal. Roentgen-rays of the chest, skull, long bones and sinuses showed nothing remarkable.

At six months of age he was taken to the Duke University Hospital, under the care of Dr. Wilbur C. Davison, who has supplied us with the pertinent information. The child's weight was only about one-half that of normal and he was 2.5 inches shorter than normal. There was generalized hypotonicity of all the muscles. There was slight fever and moderate leukocytosis. Urinalysis was negative, except for from one to three white blood cells per microscopic field. One blood culture and four urine cultures grew out a staphylococcus. The blood chemical studies revealed the following contents per 100 c.c.: phosphorus 3.6 mg., calcium 9.4 mg., non-protein nitrogen 45 mg., albumin 4.2 gm., globulin 3.5 gm. Many other studies failed to explain the child's illness.

He continued to have fever throughout the 45 days of his hospitalization, in spite of therapy with penicillin, staphylococcus antitoxin and streptomycin.

Soon after discharge from the Duke University Hospital, he began to drink excessive quantities of fluid and he developed polyuria. He drank 24 ounces of milk and 36 ounces of water daily. With a phenolsulphonphthalein test only a trace of the dye was excreted in the urine. The specific gravity of the urine was only 1.002, but after spraying pituitary powder in the nostrils it was 1.010 and it was thought that there was possibly some decrease in thirst and urine volume. This pituitary powder was used two or three times daily for about four months. On stopping this treatment no definite change in the polydipsia or polyuria was observed. His mouth always seemed to be dry and he never drooled saliva. At the age of one year the child weighed 13 pounds. At this time he could sit up, unsupported. At present the child is 17 months of age, weighs 15.7 pounds and ingests about 2,400 c.c. of fluid per day.

Not very much is known about the other three patients because they died many years ago. However, each of these individuals was a male and had polydipsia and polyuria which appeared soon after birth. One of the subjects died of kidney disease at the age of about 35. The causes of death in the other cases are not known; one of them died in infancy and the other one died during early adult life.

Discussion

It would seem probable that each of the seven individuals described had the same basic disease, but there apparently was a variation in the extent of the disturbance or in the patient's reaction to it. As seen in figure 1, the disease has appeared only in males, but has been transmitted only by females.

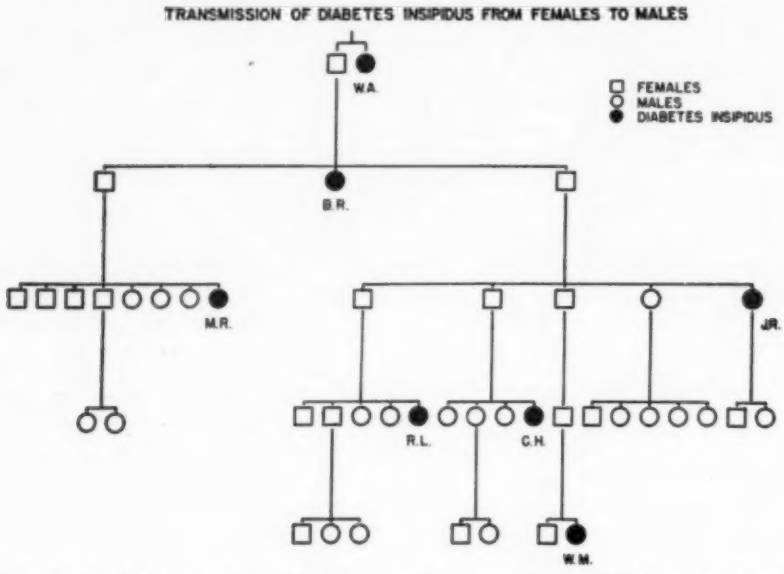


FIG. 1. This chart includes only members of the family that is affected with diabetes insipidus. There was no intermarriage in this group and no history of diabetes insipidus in their marital partners.

The manifestations of water imbalance appeared within the first few months of life. As long as an adequate supply of water was given, fairly satisfactory progress was made, although some retardation in growth occurred in all cases and two of the patients died early in life.

Marked restriction of fluid was found to produce pronounced thirst, irritability, depression, weakness and circulatory collapse. It is not surprising that such reactions should result when one considers the marked shift in water and electrolytes that occur. The ingestion of sodium chloride caused a moderate increase in thirst. On the other hand, several grams daily of potassium chloride given to one patient either had no effect or slightly decreased the quantity of urine. This patient noticed no definite effect from 20 mg. of desoxycorticosterone, or from 10 c.c. of adrenal cortical extract. None of three subjects treated with pitressin experienced a significant antidiuretic effect. In one of these patients it was demonstrated that neither his serum nor his cells inactivated pitressin within 30 minutes. Since he responded to pitressin with generalized blanching of the skin and abdominal cramps, it was suspected that his kidneys were at fault. Renal function studies revealed an impairment in the renal plasma flow and in the tubular excretion of diodrast and phenolsulphonphthalein. The glomerular filtration was slightly decreased and the filtration fraction was slightly increased. There was a marked decrease in the sodium, potassium and creatinine clearances, and a moderate decrease in the urea clearance. The patient excreted larger quantities of sodium and chloride within three hours after the intravenous infusion of normal saline than did a normal individual.

It seems likely that this patient has a physiological defect, and possibly a congenital malformation, in the loop of Henle and/or the distal convoluted tubules, thereby causing an inadequate reabsorption of water, as well as some of the other disorders of renal function mentioned in the previous paragraph. Moreover, it is presumable that a similar pathogenesis existed in the six relatives with "diabetes insipidus."

Four of the subjects had marked impairment of kidney function; in two it was not tested and in one the phenolsulphonphthalein excretion was normal. In the three subjects in which the blood pressure was estimated there was hypertension. In two individuals there was an increase in the fasting blood sugar and the brother of patient C. H. has diabetes mellitus, but not diabetes insipidus.

In analyzing the pathogenesis of diabetes insipidus, many factors must be considered, especially: (1) injury to the supraoptic nuclei, supra-optico-hypophyseal nerve tracts, or to the posterior lobe of the pituitary gland, (2) injury to the posterior portion of the hypothalamus, with particular reference to the nuclei of the tuber cinereum, and the mammillary bodies, and (3) anatomical or physiological defects in the tubules of the kidneys. On the basis of present data, which are incomplete, the clinical picture of patients with diabetes insipidus is similar in many respects regardless of the site of pathology. Moreover, the type of lesion has often remained occult. That there are variations in the characteristics of the syndrome is indicated by the many classifications that have been given.[6, 7] Veil [8] divided the cases into two groups: (*a*) hyperchloremic-hypochloruric, and (*b*) hypochloremic-hyperchloruric. The former type is the one seen more commonly and is often due to a lesion in the diencephalon. The latter type has been produced experimentally by a lesion of the fourth ventricle. In the hypochloremic-hyperchloruric type pitressin is said to have no effect.[9] Biggart [10] reported three cases of diabetes insipidus which were refractory to pitressin. He observed lesions in the tuber cinereum and he suggested that damage to tuberal nuclei might result in diabetes insipidus which is not controlled by pitressin. Moreover, some of the cases with hereditary diabetes insipidus have failed to respond to the posterior lobe principle. In view of studies on the mechanism of pitressin,[11] it is difficult to see why such cases fail to respond to this hormone, unless there is a coexisting structural defect in the kidneys. In such cases there have not been a sufficient number of reports on the physiological reactions and histological appearances of the kidneys to determine whether they contain the significant abnormality. To be sure, it is well known that polyuria may be associated with kidney disease and in some instances of tubular damage there may be such a marked loss of water and salt that a state of vascular collapse results. These patients usually do not excrete more than four or five liters of urine per day and they have a marked impairment of renal function in many respects. However, an abnormality in the loop of Henle is conceivable, which would impair reab-

sorption of water and which might not affect other renal functions to a significant extent. A congenital absence of the loop of Henle would seem possible since, phylogenetically, it was the last segment of the nephron to be added. It is present in birds and mammals, but is absent in frogs, fish and alligators. Moreover, the latter species of animals do not have a significant antidiuretic response to pitressin.[12] Since these lower animals possess all of the segments of the nephron except the loop of Henle, there is a possibility that the facultative reabsorption of water [13] that occurs in birds and mammals takes place in the loop of Henle, against osmotic gradients, as the result of a specific action by pitressin.

Therefore, it appears feasible to assume that in the cases reported above there was a congenital defect in the loop of Henle, as well as in the distal convoluted tubules, but the glomerular and proximal convoluted tubular functions were essentially normal.

Many cases of hereditary diabetes insipidus have been reported.[6] This entity is more common in boys, usually responds satisfactorily to pitressin and has not been known to be associated, etiologically, with kidney disease. Males and females have transmitted the disease. In general, hereditary diabetes insipidus has not markedly reduced life expectancy.

Summary

Seven members of one family, in five generations, were the victims of diabetes insipidus. The disease made its appearance soon after birth. It occurred only in males, was transmitted only by females, and appeared to be a sex-linked, recessive characteristic. It did not respond to pitressin therapy. The disease led to some impairment of growth and two of the individuals died early in life.

Neither the serum nor the body cells were found to inactivate pitressin any more rapidly than in normal individuals. Since one patient was observed to react to pitressin with generalized blanching and abdominal cramps, but not with a decreased polyuria, it was concluded that a physiological, and possibly an anatomical, defect in the kidneys existed. Renal function studies in this patient showed impairment in the renal plasma flow and in the tubular excretion of diodrast and of phenolsulphonphthalein. There was also a decrease in the plasma clearance of urea, sodium, potassium and creatinine. There was a slight decrease in the glomerular filtration and increase in the filtration fraction. The maximal rate of tubular glucose reabsorption was normal. Sodium chloride administered intravenously was excreted fairly rapidly. It is concluded that there probably is a congenital anomaly of the loop of Henle and the distal convoluted tubules. Although an opportunity of conducting similar renal function studies in other cases did not exist, it seems likely that they had the same type of disease. No previous reports of this syndrome have been found, although it is probable that it has existed.

BIBLIOGRAPHY

1. Ham, G. C., and Landis, E. M.: Comparison of pituitrin with antidiuretic substance found in human urine and placenta, Jr. Clin. Invest., 1942, xxi, 455.
2. Gilman, A., and Goodman, L. S.: The secretion of an antidiuretic hypophyseal hormone in response to the need for renal water conservation, Science, 1936, lxxxiv, 24.
3. Talbott, J. H.: Personal communication.
4. Goldring, W., and Chasis, H.: Hypertension and hypertensive disease, 1944, The Commonwealth Fund, New York.
5. Winer, N. J.: Renal function in diabetes insipidus, Arch. Int. Med., 1942, lxx, 61.
6. Warkany, J., and Mitchell, A. G.: Diabetes insipidus in children, Am. Jr. Dis. Child., 1939, lvii, 603.
7. Talbott, J. H.: Diabetes insipidus, Nelson Loose-Leaf Medicine, 1941, 49.
8. Veil, W. H.: Ueber die Wirkung gesteigerter Wasserzufuhr auf Blutzusammensetzung und Wasserbilanz: Beitrag zur Kenntnis der Polydipsie und des Diabetes insipidus, Deutsch. Arch. f. klin. Med., 1916, cxix, 376.
9. Bernard, C.: Leçons de physiologie expérimentale appliquée à la médecine, 1855, J.-B. Bailliere, Paris.
10. Biggart, J. H.: Anatomic basis for resistance to pituitrin (posterior pituitary preparation), Jr. Path. and Bact., 1937, xliv, 305.
11. Verney, E. B.: The secretion of pituitrin in mammals, as shown by perfusion of the isolated kidney of the dog, Proc. Roy. Soc. London, s.B. 1926, lxxxxix, 487.
12. Burgess, W. W., Harvey, A. M., and Marshall, E. K., Jr.: The site of the antidiuretic action of pituitary extract, Jr. Pharmacol. and Exper. Therap., 1933, xlix, 237.
13. Smith, H. W.: The physiology of the kidney, 1937, Oxford University Press, New York.

NON-HEMOPHILIC HEREDITARY HEMORRHAGIC DIATHESIS: REPORT OF A FAMILY OF BLEEDERS *

By Louis Levy, II, M.D., *New Orleans, Louisiana*

In 1926 von Willebrand [1] described a familial bleeding tendency affecting both sexes and characterized by a prolonged bleeding time, accompanied by a normal coagulation time and platelet count. Prior and subsequent to this report there appeared many descriptions of atypical hemorrhagic diatheses. Glanzmann [2] and others [3, 4] described an hereditary bleeding tendency, appearing in persons of both sexes, whose blood exhibited deficient clot retraction with a normal bleeding time, clotting time, and number of platelets. Buckman [5] investigated a familial hemorrhagic diathesis affecting males and females who had a prolongation of their bleeding and clotting times. A family of male and female bleeders with prolonged clotting times and normal bleeding times and platelet counts was reported by Handley and Nussbrecher.[6] A similar case was recently studied by Madison and Quick.[7] Curschmann [8] has described two families with frequent attacks of epistaxis occurring in both sexes, in the absence of hematologic abnormalities. A family with a similar hereditary bleeding tendency and normal blood findings was investigated recently by Evans and MacLaren.[9] Lombard,[10] Müller,[11] and others [12, 13, 14, 15] have investigated microscopic changes occurring in the capillaries of the nailbeds in various hemorrhagic diatheses. Since von Willebrand's reports [16] there have appeared numerous other descriptions of a similar hereditary hemorrhagic diathesis affecting males and females.[17 through 33]

We have recently studied a family of bleeders who present findings resembling those of von Willebrand's cases. The family tree is shown in figure 1. Of the 62 members, 12 males and eight females are affected. Both sexes have the bleeding tendency, and either may transmit it. Although it has been suggested that this disease is inherited through a dominant sex-linked character residing in the x chromosome, the transmission from father to son, as occurred in our cases and other reported families, would tend to exclude such a mode of inheritance.

The pertinent clinical data are presented in table 1. The age of the patients when initial symptoms appeared varied from four months to 40 years, with most patients experiencing onset of symptoms during childhood. There was a tendency toward a diminution in the bleeding episodes as the patients grew older, with the exception of one individual (number 16) in whom the bleeding persisted throughout life. All of the affected patients had bled for

* Received for publication November 29, 1946.

From the Department of Medicine, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana at New Orleans.

prolonged periods of time following minor degrees of trauma. Fifteen of the 20 patients had frequent episodes of epistaxis. Four of the eight females experienced excessive menstrual bleeding, and two had post-partal hemorrhages. Prolonged bleeding following tooth extractions occurred in four cases. Two patients had bleeding from the site of incision following appendectomy, and one patient had repeated hemorrhages following tonsillectomy. Bleeding from the gastrointestinal tract was noted in three cases. Pulmonary hemorrhages occurred in four cases. One patient experienced hematuria; a complete genito-urinary investigation revealed no pathology. Neither petechiae nor a palpable spleen were found in any of the five patients that were examined by us.

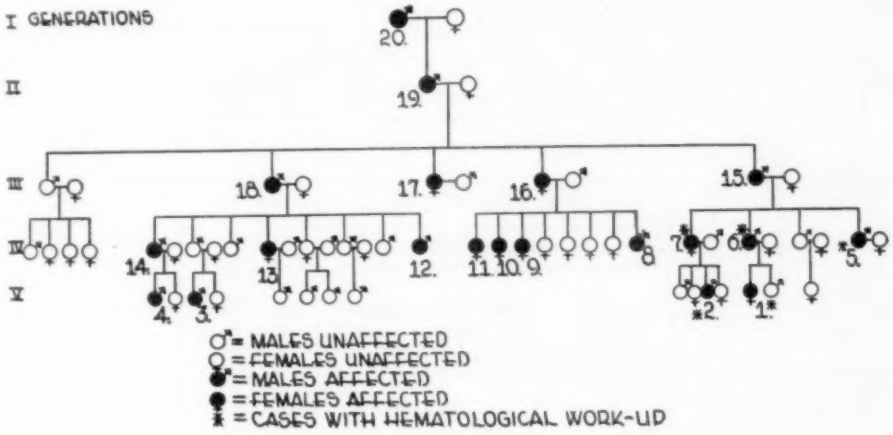


FIG. 1.

Hematological findings in the five cases studied are presented in table 2. The coagulation times of whole blood and recalcified plasma after low and high speed centrifugation, clot retraction, prothrombin time, platelet count, serum calcium, and capillary resistance were within normal limits. Bone marrow studies on one patient (number 5) revealed no abnormalities. An erythrocyte fragility test performed on the same patient was normal. Bleeding times were repeatedly determined at varying intervals, and prolongation occurred in four of the five cases. The bleeding time varied in the same individual from week to week. During periods when symptoms were present, it was usually increased. One patient (number 6) was never observed during an episode of bleeding. His bleeding time was four minutes.

Microscopic studies of the capillaries in the nailbeds of the fingers were made in three of the patients. Although a uniform picture was not observed in all of the capillaries studied, some of the capillaries in each patient's nailbeds revealed tortuosity of the capillary loops and failure of the blood cell columns to disappear after injury, the column remaining visible and terminating in the small area of extravasated blood. Abnormalities of the

TABLE I
Clinical Data

Patient*	Sex and Age	Age at Onset of Bleeding		Treatment	Cause of Death
1	F 17 yrs.	10 yrs.	Epistaxis; gums. Menorrhagia (18–21 days). Cut tongue and bled 6 hrs. Prolonged bleeding following minor trauma.	Local**	Living
2	M 12 yrs.	4 mos.	Rectal hemorrhage for 24 hrs. at age of 4½ mos. Epistaxis; gums. Bled for 24 hrs. following tooth extraction. Prolonged bleeding following minor trauma.	Transfusions and local	Living
3	M 12 yrs.	3 yrs.	Gums; epistaxis. Bled for 3 days after tonsillectomy. Prolonged bleeding following minor trauma.	Transfusions and local	Living
4	M 3 yrs.	7 mos.	Cut mouth at age of 7 mos. and bled for 20 days. Epistaxis; gums. Prolonged bleeding following minor trauma.	Transfusions and local	Living
5	M 44 yrs.	Childhood	Epistaxis. Gums. Hemoptysis. Melena. Hematuria. Prolonged bleeding following minor trauma.	Transfusions and local	Living
6	M 40 yrs.	25 yrs.	Epistaxis. Gums. Following appendectomy bled from incision for 48 hrs. Following tooth extraction bled for 72 hrs. Prolonged bleeding following minor trauma.	Transfusions and local	Living
7	F 38 yrs.	16 yrs.	Epistaxis. Gums. Following tooth extraction bled 48 hrs. Menorrhagia (18–20 days). Bled excessively during and following appendectomy. Post-partal hemorrhage (5–7 days) with each child. After giving transfusion bled 36 hrs. from needle puncture site. Prolonged bleeding following minor trauma.	Transfusions and local	Living
8	M Died	Childhood	Gums. Prolonged bleeding following minor trauma.	Local	Bled to death following gunshot wound of arm
9	F Died	Childhood	Pulmonary hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Pulmonary hemorrhage at 25 yrs.

* Number refers to numbers in figure 1.
** Packing nose; pressure bandage, etc.

TABLE I (Continued)
Clinical Data

Patient*	Sex and Age	Age at Onset of Bleeding		Treatment	Cause of Death
10	F Died	Childhood	Pulmonary hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Pulmonary hemorrhage at 30 yrs.
11	F Died	Childhood	Pulmonary hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Pulmonary hemorrhage at 25 yrs.
12	M 20 yrs.	Childhood	Epistaxis. Prolonged bleeding following minor trauma.	Local	Living
13	F 33 yrs.	Childhood	Epistaxis. Prolonged bleeding following minor trauma.	Local	Living
14	M 35 yrs.	Childhood	Epistaxis.	Local	Living
15	M Died	40 yrs.	Epistaxis. Gums. Bled for 36 hrs. following tooth extraction. Melena (10–15 times). Bled for 72 hrs. following small cut on forearm. Prolonged bleeding following minor trauma.	Local	Heart attack at 52 yrs.
16	F Died	Childhood	Menorrhagia and post-partal hemorrhage. Prolonged bleeding following minor trauma.	Transfusions and local	Uterine hemorrhage (post-partal) at 45 yrs.
17	F Died	Childhood	Epistaxis. Menorrhagia (10–12 days). Prolonged bleeding following minor trauma.	Local	Cancer of uterus at 35 yrs.
18	M Died	Childhood	Epistaxis. Gums. Prolonged bleeding following minor trauma.	Local	"Heart trouble" at 55 yrs.
19	M Died	Childhood	Epistaxis. Gums. Hematemesis. Melena. Prolonged bleeding following minor trauma.	Local	Cause of death unknown, at 97 yrs.
20	M Died	Childhood	Epistaxis. Prolonged bleeding following minor trauma.	Unknown	Unknown

capillaries have been seen in patients with mental deficiencies,[34] hypertension, hypotension, nephritis, diabetes, Raynaud's disease, acrocyanosis, clubbing of the fingers, and a variety of other conditions.

Treatment in this family consisted of local measures such as nasal packing, pressure bandages, and application of fibrin foam. Transfusions were

TABLE II

Blood Work

Patient*	1	2	5	6	7
RBC (millions/cu.mm.)	4.5	5.0	3.4	4.5	4.7
Hemoglobin (gm. %)	12.9	14.2	11.0	13.6	14.6
Hematocrit (%)	41	45	28	42	43
WBC (cu.mm.)	5,000	4,600	5,700	6,100	6,200
Polys (%)	68	61	80	70	78
Lymphocytes (%)	26	38	19	28	21
Eosinophiles (%)	0	1	—	1	1
Monocytes (%)	6	0	1	1	—
Platelets (cu.mm.)	450,000	210,000	230,000	210,000	164,000
Prothrombin Time—Quick[34] (% normal)	88	94	100	98	90
Bleeding Time—Duke[35] (min.)	8–10	4–16	4–14	4	13–22
Clotting time: Whole Blood—Lee and White[36] (min.)	3	5	6	4.5	3
Clotting time: Recalcified Plasma Slow Centrifugation[37] (sec.)	90	94	100	94	92
Clotting time: Recalcified Plasma High Speed Centrifugation[37] (sec.)	96	98	112	105	108
Clot Retraction	Start—1 hr. Complete—24 hrs.	Start—2 hrs. Complete—24 hrs.	Start—1½ hrs. Complete—24 hrs.	Start—2 hrs. Complete—24 hrs.	Start—3 hrs. Complete—24 hrs.
Rumpel-Leede Tourniquet Test	Negative	Negative	Negative	Negative	Negative
Serum Calcium (mg. %)	11.4	11.5	10.5	10	10

* Number refers to number on chart of family tree.

given during many of the episodes with questionable result as regards control of bleeding.

Five members of the family are known to have bled to death, three of pulmonary hemorrhage, one following a gunshot wound, and one of uterine bleeding. We did not have the opportunity to investigate these patients; the relative rôles of the bleeding tendency and of unrelated pathology in causing death are therefore not known.

Summary

The literature on non-hemophilic hereditary hemorrhagic diatheses is briefly summarized. A hereditary hemorrhagic diathesis affecting 20 members of a family during five generations was investigated. Both sexes were affected and either was capable of transmitting the bleeding tendency. These patients exhibited prolonged bleeding following minor trauma, with the majority experiencing epistaxis and bleeding from the gums. Bleeding from the lungs, gastrointestinal tract, urinary bladder, and uterus was also observed. Prolonged bleeding following tooth extraction, tonsillectomy, and appendectomy occurred. The only abnormal hematologic findings were a prolonged bleeding time and changes in the capillaries of the nailbeds of the fingers. Treatment consisted of local measures and transfusions. Four members died following pulmonary and uterine hemorrhages; we did not have the opportunity to investigate these patients.

I am greatly indebted to Dr. Johan T. Peters for his translation of the foreign journals.

BIBLIOGRAPHY

1. von Willebrand, E. A.: Hereditäre Pseudohemofile, Finska Läkaresällskapets Handlingar, 1926, lxviii, 87.
2. Glanzmann, E.: Hereditäre hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen, Jahrb. Kinderheilk., 1918, lxxxix, 1.
3. Kromeke, F.: Zur Frage der hereditären hämorrhagischen Diathese (Thrombasthenie), Deutsch. med. Wchnschr., 1922, xlviii, 1102–1105.
4. van der Zande, F.: Pseudohemophilia, Nederl. Tijdschr. v. Geneesk., 1923, i, 544–553.
5. Buckman, T. E.: Atypical pathological hemorrhage in early life, Am. Jr. Med. Sci., 1928, clxxv, 307–312.
6. Handley, R. S., and Nussbrecher, A. M.: Hereditary pseudohemophilia, Quart. Jr. Med., 1935, iv, 165–178.
7. Madison, F. W., and Quick, A. J.: Hemophilia-like disease in the female, with a note on the clotting time of recalcified plasma, Am. Jr. Med. Sci., 1945, ccix, 443–447.
8. Curschmann, H.: Über familiäres Nasenbluten als Ausdruck einer Pseudohämophilie, Klin. Wchnschr., 1930, ix, 677.
9. Evans, R. W., and MacLaren, H. C.: Hematuria associated with haemorrhagic diathesis, Lancet, 1945, ii, 175.
10. Lombard, W. P.: Am. Jr. Physiol., 1911, xxix, 335.
11. Müller, O.: Die Kapillaren der menschlichen Körperoberfläche in gesunden und kranken Tagen, 1922, Ferdinand Enke, Stuttgart.
12. Wright, I. S., and Duryee, A. W.: Human capillaries in health and in disease, Arch. Int. Med., 1933, lii, 545–575.

13. LEADER, S. D.: Capillary microscopy in children, Am. Jr. Dis. Child., 1932, xliv, 403–416.
14. MACFARLANE, R. G.: Critical review: The mechanism of haemostasis, Quart. Jr. Med., 1941, x, 1–29.
15. DAVIS, E.: Capillary microscopy with special reference to capillary petechiae, Am. Jr. Med. Sci., 1946, ccxii, 192–196.
16. VON WILLEBRAND, E. A.: Über hereditäre Pseudohämophilie, Acta. med. Scandinav., 1931, lxxvi, 521.
17. GEIGER, A., and EVANS, E. G.: Atypical hereditary hemorrhagic syndromes, Internat. Clin., 1938, ii, 135–157.
18. ROSLING, E.: Über hereditäre hämorrhagische Diathesen, Acta med. Scandinav., 1926, lxxii, 104.
19. ROTHMAN, P. E., and NIXON, M. K.: Familial purpura hemorrhagica without thrombopenia, Jr. Am. Med. Assoc., 1929, xciii, 15–17.
20. FARBER, J. E.: A familial hemorrhagic condition simulating hemophilia and purpura hemorrhagica, Am. Jr. Med. Sci., 1934, clxxxviii, 815–822.
21. FOWLER, W. M.: Hereditary pseudo-hemophilia, Am. Jr. Med. Sci., 1937, cxciii, 191–198.
22. BRUUN, E.: Hereditary hemorrhagic diathesis, Acta. med. Scandinav., 1939, cii, 639–648.
23. LITTLE, W. D., and AYRES, W. W.: Hemorrhagic disease; familial bleeding tendency of unusual type with splenomegaly affecting and transmitted by both males and females, Jr. Am. Med. Assoc., 1928, xci, 1251–1252.
24. KENNEDY, R. L. J.: Diseases of children benefited by splenectomy, Jr. Am. Med. Assoc., 1928, xci, 874–878.
25. SCHLICKE, C. P., and HALL, B. E.: Hereditary pseudohemophilia, Proc. Staff Meet. Mayo Clin., 1938, xiii, 529–533.
26. BAIN, C. G.: Hereditary pseudohemophilia, Northwest Med., 1939, xxxviii, 221–223.
27. SMITH, L. A., and WATKINS, C. H.: Gastric hemorrhage with hereditary pseudohemophilia. Report of a case, Proc. Staff Meet. Mayo Clin., 1941, xvi, 589–591.
28. WEEKS, E.: Familial bleeding. Report of two cases, Am. Jr. Dis. Child., 1934, xlvii, 1318–1322.
29. BAILEY, F. R., and MCALPIN, K. R.: Familial purpura. Report of two cases, Am. Jr. Med. Sci., 1935, cxc, 263–268.
30. GIFFIN, H. Z.: Unusual types of hemorrhagic diseases, Am. Jr. Med. Sci., 1928, clxxv, 44–49.
31. MINOT, B. R.: A familial hemorrhagic condition associated with prolongation of the bleeding time, Am. Jr. Med. Sci., 1928, clxxv, 301–306.
32. PERKINS, W.: Pseudohemophilia: Case study, Blood, 1946, i, 497–504.
33. ESTREN, S., SANCHEZ MEDAL, L., and DAMESHEK, W.: Pseudohemophilia, Blood, 1946, i, 504–533.
34. POWDERMAKER, F.: Capillary forms in relation to certain problems in development, Arch. Neurol. and Psych., 1929, xxii, 1207–1210.
35. QUICK, A. J.: The clinical application of the hippuric acid and the prothrombin tests, Am. Jr. Clin. Path., 1940, x, 222–223.
36. DUKE, W. W.: The relation of blood platelets to hemorrhagic disease; description of a method for determining the bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion, Jr. Am. Med. Assoc., 1910, lv, 1185–1192.
37. LEE, R. I., and WHITE, P. D.: A clinical study of the coagulation time of blood, Am. Jr. Med. Sci., 1913, cxlv, 495–503.
38. QUICK, A. J.: The diagnosis of hemophilia, Am. Jr. Med. Sci., 1941, cci, 469–474.

EXPERIENCES WITH TYROTHRICIN IN RHINOLOGY, SURGERY AND DERMATOLOGY*

By JOSEPH L. GOLDMAN, Lt. Col., MC, *New York, N. Y.*, S. A. RODDENBERRY, Capt., MC, M. P. RIZUTTO, Capt., MC, HERBERT E. FITCH, JR., Capt., MC, and MORRIS WAISMAN, Capt., MC

IN the enthusiasm with which the medical profession has accepted and used penicillin as a chemotherapeutic agent, another antibiotic substance of considerable antibacterial activity has not received the full consideration it deserves. Although tyrothricin does not possess the broad application of penicillin because it cannot be administered systemically, this drug has a definite place in the treatment of surface infections. One of the great problems which lies ahead for the medical profession will be the accurate appraisal of the various chemotherapeutic and antibacterial agents available for different infections. In the treatment of mucous membrane and skin infections and surface wounds, tyrothricin warrants trial because in some instances the offending pyogenic cocci are either more sensitive to tyrothricin than to penicillin or even resistant to penicillin and sensitive to tyrothricin. In addition, tyrothricin possesses the particular advantage of stimulating the formation of granulation tissue and epithelium.

Of special interest in connection with this subject is a recent report on the effective use of Gramicidin S in 1,500 cases in 10 leading Soviet hospitals.[1] The cases treated comprised the following groups: (1) suppuration of soft tissues, (2) preparation for skin grafting, (3) osteomyelitis, (4) empyema and peritonitis, (5) skin infections and (6) prophylactic use. Gramicidin S exhibits certain chemical and biologic properties different from those of the gramicidin of Dubos (tyrothricin is the parent substance from which gramicidin is derived), but evidently possesses similar antibacterial action.

Tyrothricin, discovered by Dubos in 1939,[2] is an antibiotic prepared from cultures of *Bacillus brevis* by extraction of the autolyzed culture with acid alcohol and precipitation of the active material from the alcoholic solution by large volumes of saline.

Tyrothricin as available commercially is a mixture of two crystalline products, gramicidin and tyrocidine. Both of these substances are polypeptides insoluble in water in the presence of electrolytes. Both exhibit antibacterial activity in vitro; tyrocidine, however, behaves like a cationic detergent and loses most of its activity in the presence of animal tissues and fluids. Gramicidin, on the contrary, retains its antibacterial activity in the presence of serum proteins and is therefore effective in vivo. Thus, it is gramicidin which is responsible for the therapeutic effects and which exerts

*Received for publication July 13, 1946.

a selective bacteriostatic and bacteriocidal effect against Gram positive cocci, gonococci and meningococci, diphtheria and diphtheroid bacilli, aerobic and anaerobic sporulating bacilli, etc., but is inactive against Gram negative bacilli.

Unfortunately, gramicidin is hemolytic and therefore cannot be introduced by the intravenous route. On the other hand, it has little or no toxic effect on other cells as exemplified by its lack of toxic action in tissue cultures. This has permitted the use of tyrothricin and gramicidin on a large scale in the treatment of bovine mastitis,[3] an infection of the udder caused by Group B streptococci. (The drug is injected directly through the teat canal into the infected udder.)

The alcoholic solution of tyrothricin is completely stable and can be kept for any length of time. Tyrothricin can be procured commercially in a 2 per cent alcoholic solution and the desired final concentration can be obtained by diluting with sterile distilled water. Electrolytes, such as sodium chloride, cannot be used as diluents because they cause precipitation of the material.

The 2 per cent alcoholic solution of tyrothricin * was used in this series, except in the very early rhinologic cases. In the early rhinologic cases, an alcoholic solution was prepared by one of us (J. L. G.) from the desiccated form of tyrothricin.†

The diluted tyrothricin was kept in the refrigerator and used only within the first five days after the preparation of the dilution. Usually fresh material was prepared every two to three days. The concentration of tyrothricin used in these cases was 0.2 mg. per cubic centimeter (1:5,000), e.g., 1 c.c. of a 2 per cent alcoholic solution of tyrothricin was added to 100 c.c. distilled water. This concentration had been found most effective in the treatment of bovine mastitis.

This study describes four separate investigations to determine the general effectiveness of tyrothricin in limited groups of (1) rhinological infections, (2) postoperative pilonidal cyst wounds, (3) minor surgical infections and (4) infectious dermatoses. Infections of the nasal mucous membrane, open and skin wounds were available for study at AAF Regional Station Hospital, Drew Field, Florida, from January 1943 to August 1944. The treatment of sinus infections described in Section I below was carried out on a small number of patients at The Mount Sinai Hospital, New York, prior to September 1942 through the coöperation of Dr. E. B. Schoenbach.

I. Observation on the Effects of Tyrothricin in Rhinology

(Lt. Colonel Joseph L. Goldman, MC)

In the field of rhinology, tyrothricin was employed in three types of cases: (1) the treatment of sinus infections, (2) direct and prophylactic treatment

* Supplied by Parke, Davis and Company, Detroit, for investigative study.
† Supplied by Dr. Dubos and Wallerstein Co., New York, for investigative study.

of postoperative sinus wounds and sinuses and (3) the prophylactic treatment of acute coryza to prevent or reduce the severity of the suppurative state.

Tyrothricin is effective in clearing quickly many acute infections of the maxillary antrum which are caused by pyogenic cocci sensitive to tyrothricin. It was not unusual to see an acute infection cured after one or two instillations of tyrothricin into the sinus. Thirty antral infections have been treated with tyrothricin during the past four years with favorable results. These infections were caused by hemolytic streptococci, pneumococci and *Staphylococcus aureus*. After washing out an antrum with warm normal saline solution, sufficient tyrothricin 1 : 5,000 was instilled to fill the antrum. The head was kept in a horizontal position for at least 15 minutes.

In my experience the instillation of tyrothricin has had no influence on chronic infections of the sinuses. If tyrothricin is instilled frequently into a chronically infected antrum, it may be difficult to isolate the causative microörganisms for a few days after the instillation. From the absence of curative effect one can deduce that tyrothricin acts only on the very surface and does not penetrate the deeper layers and glands of the diseased mucous membrane.

My experience in the postoperative treatment of antrums and ethmoidal areas has been limited but sufficient to impress me with the value of tyrothricin in these cases. In five intranasal antrotomies (three *Staphylococcus aureus*, two *Streptococcus hemolyticus*) the antrum was packed with gauze saturated with 1 : 5,000 tyrothricin and the gauze was kept moist with tyrothricin for 24 hours. This was followed by the instillation of tyrothricin into the antrum at first daily (three to four days) and then every other day (four to six days). In three instances of intranasal sphenoethmoidectomy and antrotomy, the area operated upon was packed for 24 hours with gauze saturated with tyrothricin 1 : 5,000 and then kept moist. Three cases of polypectomy and two cases in which the anterior tip of the middle turbinate and anterior ethmoidal cells were removed were treated postoperatively in a similar fashion. Beneficial effect was observed in every instance. The reaction of the tissues in the operated areas was considerably less than usually occurs. The areas exhibited very little or no exudate or polypoid swelling. The antrums, by comparison with past experience, also cleared more quickly.*

Crowe and his associates [4] have reported similar experiences with tyrothricin in these types of cases. Their method for determining the sensitivity of microörganisms to tyrothricin was used in the above cases.

The application of tyrothricin in the attempt to prevent the suppurative stage of the acute coryza has been especially gratifying. The use of bacteriocidal and bacteriostatic agents for this purpose has a bacteriologic rationale. Studies on the bacterial flora of the nose and nasopharynx made by me at The

* The writer has used penicillin 500 units per c.c. in subsequent intranasal operations and has not found this antibiotic superior to tyrothricin.

Mount Sinai Hospital, New York,[5] and at AAF Regional Station Hospital, Drew Field, Florida,[6] showed that only a small number of microörganisms of the non-pathogenic variety inhabit the normal nose (previously also reported by Jacobson and Dick[7] in a significant study), while pathogenic bacteria exist in the nasopharynx. These microörganisms, I believe, gain entry into the nose when the antibacterial defenses of the nose are inhibited during the virus phase of the acute coryza.

Ebert[8] was successful in lessening the severity of the acute coryza by spraying the nose at regular intervals with sulfathiazole powder. Schoenbach and associates were able to eliminate the *Streptococcus hemolyticus* from the rhinopharynx of carriers by using tyrothricin.

Forty patients were carefully selected for this prophylactic therapy. These consisted chiefly of members of the hospital staff at Drew Field and their families. Only patients with the history that they developed either a severe or protracted suppurative stage were given the treatment. An equal mixture of tyrothricin 1 : 5,000 and neosynephrin 1 per cent was administered in the first half of the cases and an equal mixture of tyrothricin 1 : 5,000 and privine 0.1 per cent in the second half of the series (neosynephrin ½ per cent and privine .05 per cent were employed for children and patients with pronounced vasomotor mucous membrane). Beginning with the first day of the acute coryza in most of the cases and the second day of the remaining cases, the nose was sprayed every two hours, except during sleep, in adequate amount for the solution to reach the nasopharynx. In 22 cases the suppurative stage was prevented, in 13 the suppurative phase of the acute coryza was greatly reduced in amount and duration and in five no effect was noted. The first two groups of patients were very pleased with the results.

II. Observations on the Effects of Tyrothricin in Postoperative Pilonidal Cyst Wounds

(Captains S. A. Roddenberry, MC, and M. P. Rizzuto, MC)

This is a report of clinical observations on the effect of tyrothricin on wound healing. The wounds studied were those following surgical treatment of pilonidal cysts of the sacrococcygeal area. This is not intended to be a discussion of the treatment of pilonidal cysts. These wounds being available for study, tyrothricin was employed in an effort to find a more suitable agent than those commonly used to promote rapid, healthy healing of stubborn wounds.

Daily morning dressings were done on all wounds studied. A fine mesh sterile gauze packing, saturated with 1 : 5,000 tyrothricin, was employed. Dressings were kept moist with tyrothricin irrigations every four hours. (On three cases in which penicillin solution was used, a similar technic was employed, with 500 Oxford Units of penicillin per c.c. of distilled water.)

For the purpose of reporting, cases are divided into four main groups:

1. Open wounds resulting from excision of pilonidal cysts and sinuses. This group also included excision of recurrent pilonidal cysts and excision of pilonidal cyst wounds resulting from breakdown of pilonidal cyst scars. All of these wounds following surgery were of a similar type and varied chiefly in size and shape.

2. Open wounds resulting from infection and breakdown following primary closure after excision of pilonidal cyst. When gross infection was recognized in any wound, all sutures were removed and the wound was opened and packed.

3. Abscess cavities resulting from incision and drainage of sacrococcygeal abscesses. Included in this group were cases of abscess formations which were of known pilonidal cyst origin, manifested by the presence of sinus openings, fistulous tracts and hair. Included, also, were cases in which this evidence was lacking but in which a presumptive diagnosis of pilonidal cyst was made because of the typical location and appearance of the abscess.

4. Miscellaneous cases which included a heterogeneous group of pilonidal cyst wounds. This group embraced minor wound complications following excision and primary closure such as slight separation of skin edges, stitch abscess and breakdown of previously healed wound with separation of wound margins.

Material. *In Group I* there were 29 cases, 15 of which were treated with tyrothricin alone, employing the technic described above.

The granulations of these wounds assumed a smooth salmon pink to cherry red color. As a rule, these granulations bled easily on pressure, were painless to touch and presented only slight mucoid drainage on the dressing. The amount of drainage from these wounds was minimal in comparison with previous wounds treated with other substances. Healing was more rapid and the margins of the wounds, characteristically, were surrounded by a bluish-white film of epithelium growing centripetally and attaching itself firmly to the granulations in its progress. Measurements of the wounds were taken periodically in an effort to record the actual rate of healing and the total healing time. This policy was soon abandoned because the variation in size and contour of wounds made accurate measurements impossible. Healing time was tabulated but due to the multiplicity of uncontrollable and variable factors between individual wounds, a detailed statistical report is not being offered. This seemed to us to be invalid and misleading. In general, healing was enhanced in this group and the wounds maintained a healthy, clean appearance throughout.

In six cases penicillin was employed and a similar technic followed. Penicillin was used locally in a 500 unit per c.c. solution for 20 days on these cases. Because of an acute shortage of penicillin, the treatment was completed with tyrothricin. Clinically the wounds under the influence of penicillin reacted in a manner similar to those in which tyrothricin was used alone. Healing was rapid and no significant change in the rate of healing

was noted following the shift from penicillin to tyrothricin. It was observed that in wounds under the influence of penicillin there was a greater amount of mucoid drainage on the dressing than in those in which tyrothricin was used. Also, the wounds treated with penicillin lacked the healthy appearance noted in the cases treated with tyrothricin and granulations exhibited a paler appearance. Dressings in the cases treated with penicillin were accompanied by more pain for the first postoperative week.

In eight cases various other substances were used. Plain saline packing was employed in two cases. These granulating wounds presented considerable mucopurulent drainage and were more sensitive to the touch for the first four days. The granulations were pale and did not bleed easily. Healing progressed rather slowly when compared with the above cases.

Three cases received azochloramide packing. The granulations were similar to those in which saline was employed. After using this solution for two and one-half weeks, one case developed urticaria and the treatment was discontinued. Patch test was positive in this case.

In one case vaseline gauze packing was used. Exudation and drainage were marked in this wound. The granulations remained pale and rather sensitive to the touch throughout the treatment. Healing was slow.

In two cases vaseline gauze, sprinkled with sulfanilamide powder, was used. The exudation seemed to be less and the granulations appeared healthier than in the last case. But healing progressed slowly as compared with the tyrothricin cases.

In Group II there were seven cases. All these cases had primary closure of the wound after excision of the pilonidal cyst and sinus. Cotton sutures were used in all cases. Ranging from the third to fifth postoperative day, the wounds became infected and were accompanied by pain, a rise in temperature and in three cases by a foul discharge. All these wounds were grossly infected. The sutures were removed, the wounds opened and packed with tyrothricin in the manner previously described. Within 24 to 48 hours, drainage ceased and the wounds assumed a clean, healthy appearance, and healed rapidly, maintaining the characteristics of the tyrothricin-treated wounds described in Group I.

In Group III there were 21 cases. Tyrothricin was used in the treatment of all the patients in this group. This was the group of acute abscess of the sacrococcygeal area. These cases were treated by incision and drainage. The pus evacuated was typically of a thick granular nature, foul smelling and was indicative of marked tissue destruction. The cavities varied in size but were usually large. These wounds were treated with tyrothricin in the routine manner. The effect of tyrothricin in this group of cases was very good. The wounds healed by granulation and the appearance of the wound surface was the same as in the cases described in Group I.

There were five cases *in Group IV*. The wounds were all small, varying from the size of a navy bean to a buckshot. These wounds were small areas

of separation of previously healed wounds, overlapping of skin edges and small sinuses originating from infection around nonabsorbable sutures. There was no apparent advantage in these cases from the use of tyrothricin insofar as the rapidity of healing was concerned. The wounds did appear cleaner, but healing did not progress until the basic difficulty was removed (e.g., the removal of suture, cauterization of overlapping skin margins, etc.).

Bacteriology. The method of culturing wounds was as follows:

An initial culture was inoculated at the time of operation, followed by a daily culture for the first three postoperative days, taken when dressings were changed. Subsequent cultures were usually taken at weekly intervals or when the indication arose. The predominant microörganisms found on the initial cultures were *Staphylococcus aureus* of the hemolytic and nonhemolytic varieties. Occasional cases showed beta hemolytic streptococci or a mixture of streptococci and staphylococci. Following the use of tyrothricin, there was a change in the flora of the wounds to *B. proteus* in the majority of cases within three to five days. In Group I, of the 15 cases treated with tyrothricin, 13 cases showed pure cultures of *B. proteus.* In Group II, of the eight cases in which tyrothricin was used, five cases showed *B. proteus* as the only microörganism grown. Of the 20 cases in Group III, following the use of tyrothricin, 17 cases showed *B. proteus* as the only remaining microörganism. Of the five cases in Group IV, there were two cases from which *B. proteus* was cultured following the use of tyrothricin.

These findings indicate that tyrothricin used under the conditions described above was an effective bacteriostatic substance for the microörganisms we had been accustomed to isolate from these wounds. *B. proteus* is usually a non-pathogenic microörganism and since this was the principal microörganism cultured following the use of tyrothricin, we feel that this is supporting evidence for our clinical impressions of wound healing already described.

Summary. The authors of this section of the present report were in charge of a pilonidal cyst ward from October 1, 1943 to September 19, 1945. During this period there were 185 admissions. These included pilonidal cysts with sinuses, recurrent pilonidal cysts, wounds from breakdown of pilonidal cyst scars and acute abscess arising in pilonidal cysts. In an effort to find a more suitable agent than those previously used to promote rapid, healthy healing of open granulating wounds, tyrothricin was employed. From our observations, the following conclusions were made:

1. Tyrothricin used locally on wounds following surgery on pilonidal cysts was superior in its effects on healing to any substance we had used previously.
2. The granulation tissue was cleaner and healthier and the rate of wound healing appeared to be more rapid.
3. Clinically, tyrothricin produced no injurious results on granulating

wounds and no untoward systemic effects were encountered in the cases studied.

4. The usual mixture of pathogenic microörganisms found to be present on wound cultures prior to use of tyrothricin was reduced in the majority of cases to the single microörganism, *B. proteus*, following the use of this substance.

5. Next to tyrothricin, the most effective substance used was penicillin.

III. Observations on the Effects of Tyrothricin in Minor Surgery

(Captain Herbert E. Fitch, Jr., MC)

Tyrothricin has proved to be an important addition to our armamentarium in the treatment of minor surgical infections. The preparation is of outstanding value in its antibacterial effect as well as its property of stimulating healing by the formation of granulation tissue.

In the following cases to be reported, treatment was according to well established surgical principles. First, localization of fluctuation was established by the application of moist heat to the area of inflammation. Secondly, with intravenous or local block anesthesia, adequate surgical drainage was afforded. Thirdly, a culture was secured in order that the infecting organisms might be identified. Finally, the specific measures were taken to apply the drug to the affected areas.

After incision of the fluctuant area and removal of exudate with gentle debridement of necrotic tissue were accomplished, a plain gauze saturated with 1 : 5,000 tyrothricin solution was loosely packed in the wound. The pack was moistened with tyrothricin solution at intervals of four hours by using a bulb syringe, taking care not to dislodge the dressing. This procedure was carried out for 48 hours, at which time the pack was removed and the wound inspected. The pack was reinserted if it was deemed necessary, but usually only a small wick soaked with tyrothricin inserted between the skin edges was required. On the fourth day after operation dry dressings were usually sufficient and remained so until the patient was discharged from the hospital.

The observations and impressions gathered from the use of this agent can be summarized as follows: (1) There was a change in the character of the exudate in the first 24 hour period. This consisted of a lessening of the thick, purulent discharge with the appearance of a thin, almost colorless exudate. (2) There was a marked diminution or cessation of exudate in 72 hours. (3) There was a rapid development of healthy granulations with a clean appearance of the entire wound. (4) Epithelialization occurred early and complete healing was rapid.

Prompt diminution of the exudate was quite remarkable with this agent. The grayish-white appearance at the base of wounds resulting from incision

and debridement of carbuncles was not found. Rather, there was a clean, pink, healthy base with little or no discharge after 48 hours. The granulations were never exuberant enough to require removal by surgery or cautery. Scarring which resulted seemed to have been minimal.

Summary of Cases. 1. Cellulitis of the leg: 23 cases. Microörganism usually found, *Staphylococcus aureus.* Tyrothricin used for four days as a rule. Average length of stay in hospital after incision and drainage nine days.

2. Cellulitis of the hand and fingers: seven cases (two with infection of palmar space). Microörganism: *Staphylococcus aureus.* Average stay in hospital 12 days, 19 days for the palmar space infections, with minimal scarring and no contractures.

3. Carbuncles: six cases. Microörganism: *Staphylococcus aureus.* Rapid healing and minimal scarring. Hospitalization averaged 12 days.

4. Suppurative paronychia: (treated after removal of the nail) five cases. Rapid healing of the nail bed. No culture on these cases.

5. Furunculosis: two cases. Good results only on the incised furuncles. No effect noted on the unopened lesions.

IV. Observations on the Effects of Tyrothricin in a Limited Group of Infectious Dermatoses

(Captain Morris Waisman, MC)

A brief experience with tyrothricin in dermatologic treatment has yielded a distinctly favorable impression of its value. Because of the small number of patients studied, statistical evaluation is precluded. It is hoped that the agent will become available at military hospitals where its efficacy in the treatment of dermatologic diseases, not ordinarily a cause for hospitalization in civilian practice, may be adequately appraised.

My clinical material was divided into two groups: (1) pustular infections, represented by two cases of severe folliculitis, and (2) eczematoid pyodermas, represented by a series of nine patients with superficial cutaneous lesions either the site of initial bacterial infection or secondarily infected. The secondarily infected eruptions usually were superimposed on preëxisting dermatophytosis of the feet. Cultures were taken in most cases.

The cases of pustular folliculitis, one of the beard and the other of the legs, from each of which a culture of hemolytic *Staphylococcus aureus* was isolated, showed no healing with application of tyrothricin wet dressings. (The deep folliculitides are notoriously refractory to therapy.) Neither did these cases respond to the use of conventional antiseptics, nor to penicillin and sulfonamides topically and systemically. Some benefit was gained by rupture of the pustules preliminary to application of the tyrothricin solution but satisfactory healing failed to take place. It was concluded that the inability of the agent to penetrate to the depth established by the infection in the hair follicles accounted at least in part for the poor result.

Excellent results were seen in six of nine cases of what I shall call "infected eczematoid dermatitis," to include both primary infection of the skin (Engman type and diffuse impetiginous eruptions) and secondarily infected dermatoses, notably dermatophytosis, dermatophytids and contact dermatitis (the latter often due to overtreatment of dermatophytosis). Culture in most cases disclosed the presence of hemolytic *Staphylococcus aureus* (coagulase and/or mannite positive), alone or in association with beta hemolytic streptococci. Most lesions were confined to the toes and feet, where they were characterized by dusky erythema and edema, often with well-defined borders, and exhibiting denudation of epithelium, excoriations, fissures, oozing, crusting and scaling, and scattered pustules of a peripheral overhanging ("dissecting") epidermal collarette. This condition commonly complicated dermatophytosis of the feet in troops stationed in Florida. The infection was an extremely indolent one, very resistant to treatment as a rule, often manifesting intolerance to the application of greases in any form, becoming excessively dried and irritated by alcoholic tinctures, prone to develop allergic sensitization to many topical medications (and possibly to its own autolytic products), and exhibiting multiple recrudescences and recurrences. As a group it constituted one of the most difficult therapeutic problems I had encountered.

The results obtained with 1:5,000 tyrothricin solution in the latter group of cases is therefore very dramatic, in that healing occurred in one-quarter to one-half of the time ordinarily expected and, what is just as remarkable, with no evidence of irritation of the skin and with good tissue repair, so that there were no recurrences observed among the healed cases.

Among the merits of tyrothricin in my experience must be listed freedom from irritation, rapidity of action, and specificity, as indicated by its success in lesions unresponsive to other potent bactericides, including the sulfonamides and penicillin. Worthy of investigation would be (1) determination of the antibacterial properties of tyrothricin incorporated in various types of bases, (2) establishment of minimal effective concentrations for economical and optimal utilization, and (3) evaluation of additive or synergistic effects obtained when tyrothricin is used concurrently with other antibacterial agents, topical or systemic.

General Summary

1. Three types of cases have been presented which have been treated with tyrothricin locally. The cases comprise (1) rhinological infections, (2) surgical infections and (3) dermatological infections.

2. In the rhinological group, tyrothricin was used (1) in the treatment of sinus infections, (2) in the direct and prophylactic treatment of postoperative sinus wounds and sinuses and (3) in the prophylactic treatment of acute coryza to prevent or reduce the severity of the suppurative stage.

3. In the surgical group, tyrothricin was used (1) in a series of pilonidal cases and (2) in a series of minor surgical infections.

4. In the dermatological group, tyrothricin was used on a series of resistant infections.

5. The concentration of tyrothricin used in these cases was 0.2 mg. per c.c. (1:5,000), e.g., 1 c.c. of a 2 per cent alcoholic solution of tyrothricin was added to 100 c.c. distilled water.

6. In this study tyrothricin was found to be an effective antibiotic in controlling and preventing surface infection.

BIBLIOGRAPHY

1. Sergieve, P. G.: Clinical use of gramicidin S, Lancet, 1944, ii, 717.
2. Dubos, R. J.: Bacteriocidal effect of an extract of a soil bacillus on gram positive cocci, Proc. Soc. Exper. Biol. and Med., 1939, xl, 311–312.
   Dubos, R. J., and Hotchkiss, R. D.: The production of bacteriocidal substances by aerobic sporulating bacilli, Jr. Exper. Med., 1941, lxxiii, 629–640.
   Dubos, R. J., and Hotchkiss, R. D.: Origin, nature and properties of gramicidin and tyrocidine, Trans. and Stud. Coll. Phys. of Phila., 1942, x, 11–18.
3. Little, R. B., Dubos, R. J., and Hotchkiss, R. D.: Gramicidin, novoxil and acriflavine for the treatment of the chronic form of streptococcic mastitis, Jr. Am. Vet. Assoc., 1941, xcviii, 189–199.
   Little, R. B., Dubos, R. J., Hotchkiss, R. D., Bean, C. W., and Miller, W. T.: The use of gramicidin and other agents for the elimination of the chronic form of bovine mastitis, Jr. Vet. Res., 1941, xi, 305–312.
   Schalm, W. W.: Treatment of bovine mastitis, Jr. Am. Vet. Med. Assoc., 1941, xcix, 196.
4. Crowe, S. J., Fisher, A. M., Ward, A. T., Jr., and Foley, M. K.: Penicillin and tyrothricin in otolaryngology, Ann. Otol., Rhinol. and Laryng., 1943, lii, 541–572.
5. Goldman, J. L.: Bacteriology of nose, sinuses and nasopharynx (Proceedings of Seminars on Recent Advances in Bacteriology and Immunology with Clinical Considerations, Gregory Shwartzman, M.D., Chairman), Jr. Mt. Sinai Hosp., 1943, ix, 921–927.
6. Goldman, J. L.: To be published.
7. Jacobson, L. O., and Dick, G. F.: Normal and abnormal flora of the nose, Jr. Am. Med. Assoc., 1941, cxvii, 2222–2225.
8. Ebert, E.: Local treatment of acute rhinitis with sulfathiazole, Arch. Otolaryng., 1943, xxxviii, 324–327.
9. Schoenbach, E. B., Enders, J. F., and Mueller, J. H.: The apparent effect of tyrothricin on *Streptococcus hemolyticus* in the rhinopharynx of carriers, Science, 1941, xciv, 217–218.

CASE REPORTS

POLYOSTOTIC FIBROUS DYSPLASIA IN ONE OF NEGRO TWIN GIRLS *

By Guy A. Caldwell, M.D., *New Orleans, Louisiana,* and T. F. Broderick, Jr., M.D., *Boston, Massachusetts*

Introduction

Interest in cystic lesions of bone was greatly stimulated by the successful removal of a parathyroid adenoma by Mandl [1] in 1925. Since that time generalized osteitis fibrosa cystica of von Recklinghausen has been recognized as due to adenoma or hypertrophy of the parathyroid glands. However, the occurrence of other cystic bone lesions, either generalized or localized, without obvious abnormality of calcium and phosphorus metabolism, has been noted with increasing frequency and has aroused considerable speculation as to the nature of this condition or variety of conditions.

In 1937 Albright, Butler, Hampton and Smith [2] called attention to a syndrome characterized by (a) "A disseminated osteitis fibrosa (both hyper- and hypo-ostotic), with a distribution suggesting a relationship between the lesions and the nerve roots or to an embryologic defect in the myotomes; (b) areas of cutaneous pigmentation which have a distribution suggesting some connection between them and the bone lesions; (c) sexual and somatic precocity especially, if not exclusively, when the disease occurs in the female sex." Five cases were reported, 13 cases from the literature were reviewed and one published case was cited. Several of these had been unsuccessfully explored for parathyroid adenomata. Subsequently, there have been reported or resurrected from the literature over 50 cases which display the features of this syndrome and establish it as an entity.

In their review of the literature, Gorham and his co-workers [3] found that at least seven examples of the syndrome had been reported in females and five in males before Albright's paper appeared. The precocious puberty, however, was not evident in the males. Among the case designations were: "Precocious puberty and bone fragility" by Weil [4] in 1922; "Osteitis fibrosa cystica generalisata (osteodystrophia fibrosa)" by Priesel and Wagner [5] in 1932; an atypical form of "von Recklinghausen's neurofibromatosis of bones" by Snapper and Parisel [6] in 1933 and "Juvenile Paget's disease" by Hummel [7] in 1934. "Fibrocystic osteitis with abnormal localization and evolution" was reported by Pagniez, Plichet and Fauvet [8] in 1938 in apparent unawareness of Albright's description of the syndrome in 1937. Since 1937 most of the cases have been reported as "Albright's syndrome" but Albright [9] feels that "Polyostotic fibrous dysplasia," as employed by Lichtenstein [10a, 10b] in 1938, is a more appropriate designation.

* Received for publication May 9, 1946.
From the Tulane Orthopedic Service, Charity Hospital of Louisiana at New Orleans.

A negro girl, one of proved dizygotic twins, who manifested all the features of the complete form of this syndrome, has been observed over a period of 20 months. The case is presented as another example of polyostotic fibrous dysplasia which has special interest because of its occurrence in a negro and in but one of twins.

Case Report

History: A nine year old negro girl was first seen at Charity Hospital in New Orleans on February 12, 1944. One day previously, in a neighboring town, she had sustained a slight fall with the result that she could not move her leg although pain was only moderate. An emergency splint was applied and transfer to New Orleans

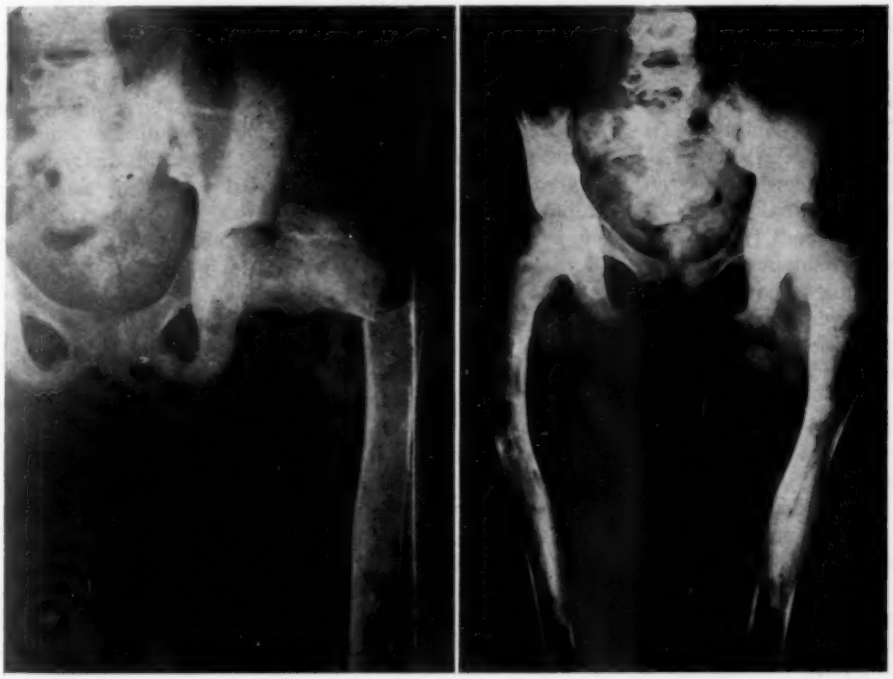


Fig. 1. (*Left*) February 12, 1944. Pathological fracture of left femur. Note pseudocystic and sclerotic areas throughout the pelvis and femur.
Fig. 2. (*Right*) January 10, 1945. Note healed fracture (10 months a.i.) and scattered pseudocystic areas, more numerous on the right side.

advised. On arrival she complained of little discomfort, although there was obvious shortening and external rotation of the left leg in the Thomas splint. Roentgenograms (figure 1) showed a subtrochanteric fracture of the left femur as well as areas of rarefaction and sclerosis throughout the pelvis and both femurs. Bilateral Russell's traction was applied.

Physical Examination: The patient was a tall, slender apathetic negro girl in no apparent distress who appeared to be adolescent rather than the stated age of nine years. The head was large, with increased transverse diameter of the skull and prominent frontal bosses, making the face appear relatively small and wedge-shaped. Facial movements were symmetrical but somewhat decreased in excursion. The

hair was fine, dry, brownish-black and kinky. The eyes were set wide apart, and some proptosis of the right eyeball as compared to the left was evident. The pupils reacted to light and distance. The right pupil measured 4 mm. in diameter and the left 4.5 mm. Ophthalmoscopic examination revealed atrophy of almost the entire right optic disk and of the temporal portion of the left optic disk. The vessels were normal in appearance, and neither hemorrhage nor exudation was observed. Visual coördination was poor, and visual field examination showed gross impairment for the left eye and almost complete blindness in the right eye. The nose was broad, more so than is racially normal, and the bridge was depressed. The throat, tonsils, teeth and tongue were normal. No buccal pigmentation was observed. The neck was symmetrical, and no lymph nodes were palpable. The thyroid gland could be easily palpated, but it was not obviously enlarged nor were any nodules or irregularities discernible. The thorax was noticeably asymmetrical, being more prominent on the right, and respiratory excursion was greater on that side. Breath sounds were vesicular throughout. The heart was not enlarged. Apical and pulse rates were 80 beats per minute and rhythm was regular. No murmurs were heard. Blood pressure was 118 mm. of Hg systolic and 78 diastolic. The breasts were adolescent in size and contour. The right breast and its areola were more prominent than the left breast. Axillary and pubic hair was adolescent in amount and distribution. The abdomen showed no abnormalities. The general sexual development was compatible with that of a 14 year old girl. The clitoris was enlarged to pubertal size. The hymenal ring was present but relaxed. A vaginal examination was not done. Rectal examination showed the uterus to be infantile in size and acutely anteflexed. The adnexa could not be palpated. During six months of hospitalization the patient had never menstruated nor, according to the family, had menarche occurred. The extremities were grossly normal. The abdominal reflexes were present. Knee and ankle jerks were active and equal. Plantar reflexes were normal.

The skin was light brown with several patches of discoloration. Paler areas were evident over the brow and both malar bones, as though the skin were under some tension. Several black, circumscribed spots of increased pigmentation were scattered over the lower thoracic and lumbar spines, the largest of which measured 3 cm. in diameter. A saddle area of black pigmentation measuring 9 by 12 cm. extended out from the sacrum over the right buttock. No sensory changes were demonstrable in the skin of these pigmented areas.

Course: Bilateral Russell's traction was maintained for five weeks following which the patient was discharged in a 1½ spica cast. This was removed five weeks later and ambulation with crutches was permitted. The crutches were discarded after one month, and normal activity was resumed. Interval roentgenograms showed healing of the fracture but persistence of the bony lesions (figure 2).

The patient has been observed at frequent intervals over the past 20 months and additional pertinent data obtained. An attack of mumps which developed in March 1944 is worthy of note in relation to the endocrine disturbance. There have been several obvious changes in her general physical condition. Progressive enlargement of the skull with more conspicuous "wedging" of the face has been evident. Also the sexual maturity has become more apparent, but menarche has not appeared.

Biopsy: Biopsy material from the right ileum, left tibia and skin from the pigmented area on the right buttock was obtained on January 24, 1945. The specimens were sent to Dr. Granville A. Bennett,[11] Professor of Pathology at the University of Illinois College of Medicine, who made and commented on the slides which Dr. Charles E. Dunlap,[12] Professor of Pathology at the Tulane University School of Medicine, described as follows:

"No. 1 Bone from right ileum (figure 3). The major portion of the slide shows an irregular pattern of dense, closely packed, irregular trabeculae of bone. These

trabeculae are heavily calcified centrally but are bordered by a paler zone of osteoid tissue. The peripheral boundaries of the osteoid are frequently irregular and indefinite. Calcification extends from the central areas into the osteoid in a ragged fashion and the cement lines and canaliculi are not clearly defined for the most part. These changes in bone structure extend to the periosteum and no normal cortical bone remains. The marrow spaces are solidly filled with cellular fibrous tissue containing relatively little collagen. Along the margins of all the trabeculae, osteoclastic and osteoblastic activity is vigorous. At one end of the section, a chondro-osseous

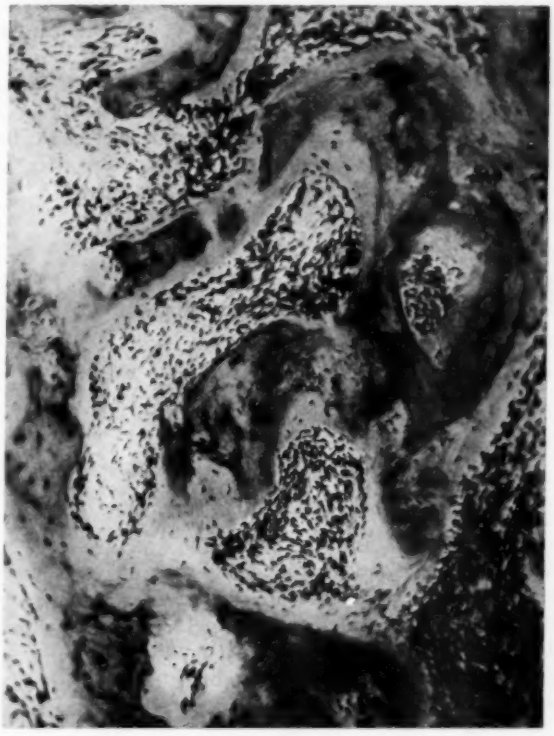


FIG. 3. Photomicrograph of bone. Magnification × 150. The trabeculae are irregular and closely packed. Each shows a central region of heavy calcification and a peripheral layer of osteoid. The marrow spaces are filled with cellular fibrous tissue.

junction is present. There is evidence of slight endochondral bone formation. Along the margin of the section farthest distant from the periosteum, the abnormalities in the bone and bone marrow terminate abruptly and give way to relatively normal bone. The marrow here is cellular and relatively normal except for the presence of many eosinophilic cells of the myelocytic series. The periosteum near the chondro-osseous junction is thicker than normal and extremely cellular, resembling the abnormal fibrous tissue present in the marrow spaces.

"*No. 2 Skin.* There is slight hyperkeratosis present particularly in numerous minor invaginations of the skin surface. The epithelial layer is thin. The basal cells contain heavy deposits of melanin. The dermal connective tissue and skin appendages are not remarkable. This section is not distinguishable from heavily pigmented normal negro skin.

"No. 3 Fragments of bone near tibial tubercle. The slide shows for the most part cortical bone of normal structure. At one point, a marrow space is filled with fibrous tissue and some reabsorption of cortical bone is apparent together with a few of the atypical trabeculae described in slide No. 1."

Psychometric Examination: A psychometric examination on April 13, 1945, with the revised Stanford-Binet Scale—form L, indicated that the patient was a low grade moron. Coördination and motor control were poor. She did better on verbal tests than on performance tests. The examiner felt that she displayed many stigmata associated with a feebleminded child.

Laboratory Studies: Representative laboratory findings from February 1944 to October 1945 are: 3,600,000 erythrocytes per cu. mm.; hemoglobin 64 per cent; 6,400 leukocytes per cu. mm.; sedimentation rate 18 mm. per hr. (Wintrobe); urinalysis, normal; urine smears and cultures normal; no Bence Jones proteinuria; urea nitrogen 10 mg. per 100 c.c.; serum protein 6.2 gm. per 100 c.c.; icterus index 13 units; glucose 111 mg. per 100 c.c.; chlorides 685 mg. per 100 c.c. plasma; cholesterol 161–217 mg. per 100 c.c. plasma. Serologic tests for syphilis and skin tests for tuberculosis gave negative reactions.

Blood chemistry studies showed:

	Calcium	*Phosphorus*	*Alkaline Phosphatase*
2/15/44	10.9 mg. per 100 c.c.	5.3 mg. per 100 c.c.	26.7 Bodansky Units
2/21/44		5.0	17.2
3/13/44		4.1	19.1
5/31/44		5.25	34.7
2/ 6/45		4.8	25.4
4/19/45	12.0	4.4	26.1
6/13/45		4.5	
8/13/45	10.0	4.0	36.0

Phenolsulphonphthalein excretion was normal.

Cystoscopic examination showed a normal lower urinary tract. Roentgenograms of the kidney, ureters and bladder demonstrated kidney shadows normal in size, shape, and position. Neither calculi nor calcifications were seen. The pelves, calyces and ureters on both sides appeared to fill in a normal manner.

Satisfactory determination of the basal metabolic rate on February 20, 1945 was plus 24. Two subsequent tests gave unsatisfactory results because of poor coöperation.

Electrocardiography: An electrocardiogram on February 14, 1945 showed nothing more than sinus tachycardia.

Lumbar Puncture: Lumbar puncture on September 20, 1945 showed crystal clear fluid with a pressure of 90 to 120 mm. of water. The dynamics were normal and the Queckenstedt and Tobey-Ayer tests gave negative results. Protein, 26; glucose, 66; Pandy's test and serologic reactions were negative; cell count was 4 per cu. mm.; colloidal gold curve was normal (i.e. 1120000000).

Roentgenography: Complete skeletal examination has shown multiple, asymmetrically scattered areas of decreased density and sclerosis (figure 4). The skull revealed dolichocephaly (figure 5), pronounced thickening of the bones of the vault, particularly in the base with sclerosis in this region, and some few areas of decreased density within the vault. Marked sclerosis of the sphenoid bone was apparent, but the sella turcica did not appear to be enlarged. Roentgenograms of the chest were normal except for some areas of decreased density throughout the ribs. Small cystic areas were seen in most of the various bones of the extremities (figures 6 and 7). Dental roentgenograms showed calcification of the midline palate, osteoporosis of the

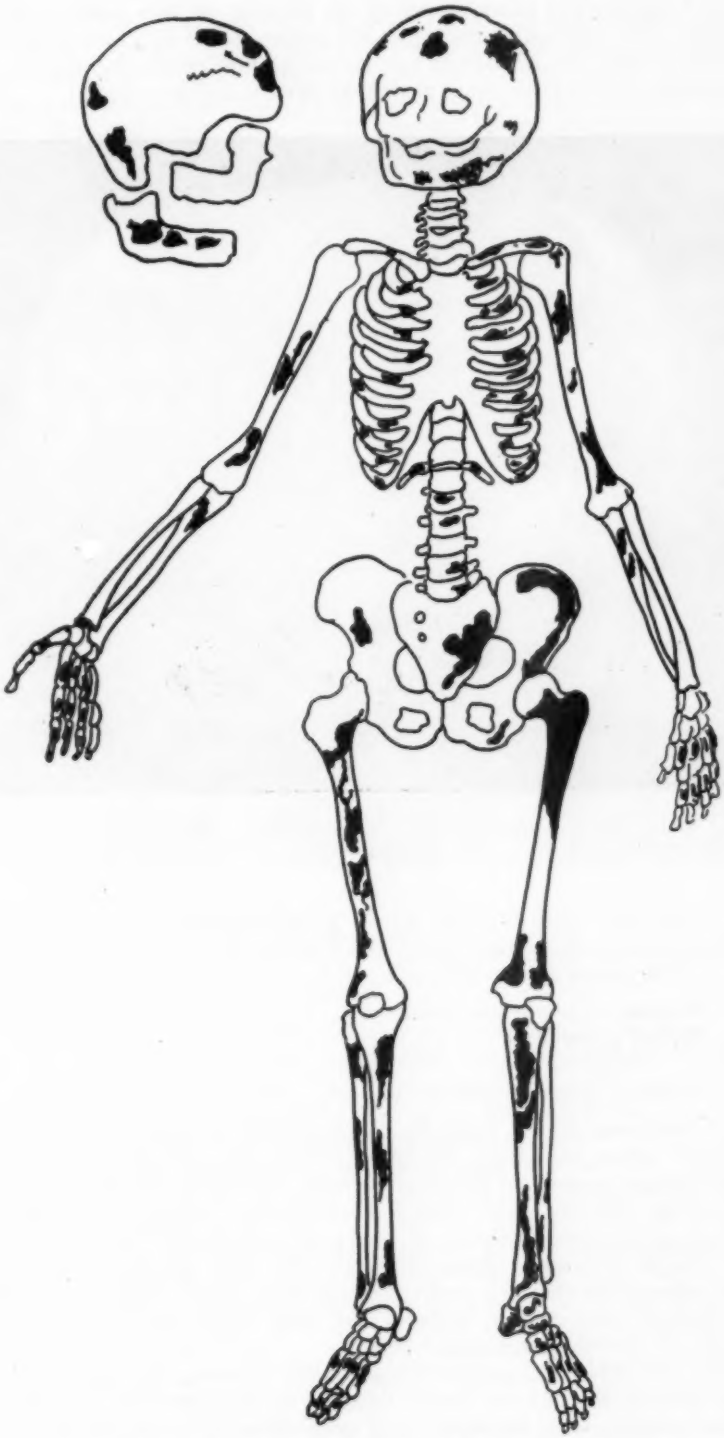


FIG. 4. Diagram showing areas of bone lesions.

mandible and maxilla and protuberance of the maxilla on both sides. Well formed second molars with eruption of the lower left second molar indicated a dental age of 13 to 14 years (figure 5). Study of various ossification centers revealed a bone age of 13 to 14 years, two to three years more than her chronologic age.

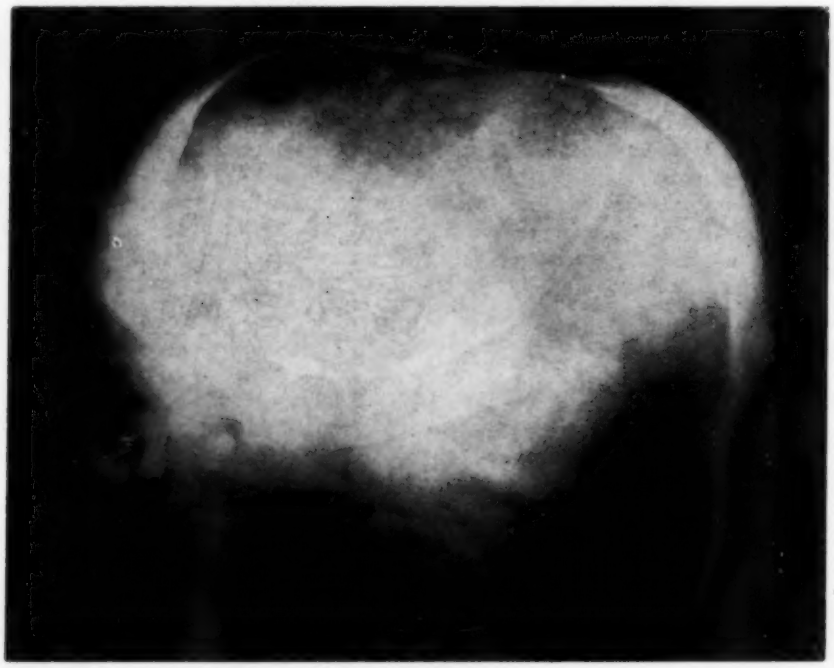


FIG. 5. Skull showing dolichocephaly, thickening of vault with a few areas of decreased density, and sclerosis of the sphenoid bone. Note presence of lower left second molar.

Course: In April 1945 the patient was given aluminum acetate solution orally, 1 dram three times a day after meals, supplied by Mr. A. P. Lauve, the hospital pharmacist. The preparation contained:

Solution of aluminum subacetate	545 c.c.
Glacial acetic acid	15 c.c.
Water, a sufficient quantity to make	1000 c.c.

The use of aluminum acetate followed the suggestion of Helfet [13] that the solution possibly might reduce phosphorus intake by precipitating phosphates in the intestinal tract with resultant increase in calcium retention. Ghormley and Hinchey,[14] although undecided as to the physiologic action of aluminum acetate, were able to show definite roentgenographic evidence of improved calcification in a series of cases. After this patient had taken aluminum acetate for three months, her father volunteered the information that she could "see and hear better than ever before." No objective changes were evident, however, nor were there any changes in either the blood chemistry or roentgenograms.

On May 27, 1945 the patient tripped while playing and sustained a simple transverse fracture through the lower third of the left humerus (figure 8). This was reduced under general anesthesia and immobilized for eight weeks in a hanging cast. Healing was rapid, with some excess callus formation.

Family History: The parents were unaware of any anomalous conditions on either side of the family. The mother and father are now 43 and 39 years old respectively. There are eight children: a 15 year old daughter; the 11 year old patient and her twin sister; eight year old twin boys; a five year old son; a three year old girl and a 1½ year old baby girl. Other than the patient no one in the family has had any serious or unusual illness.

The Twin Sister: Studies were made to determine whether the twins were monozygotic or dizygotic since it was hoped that the differentiation might clarify the nature of this obscure condition. However, examination of several traits which

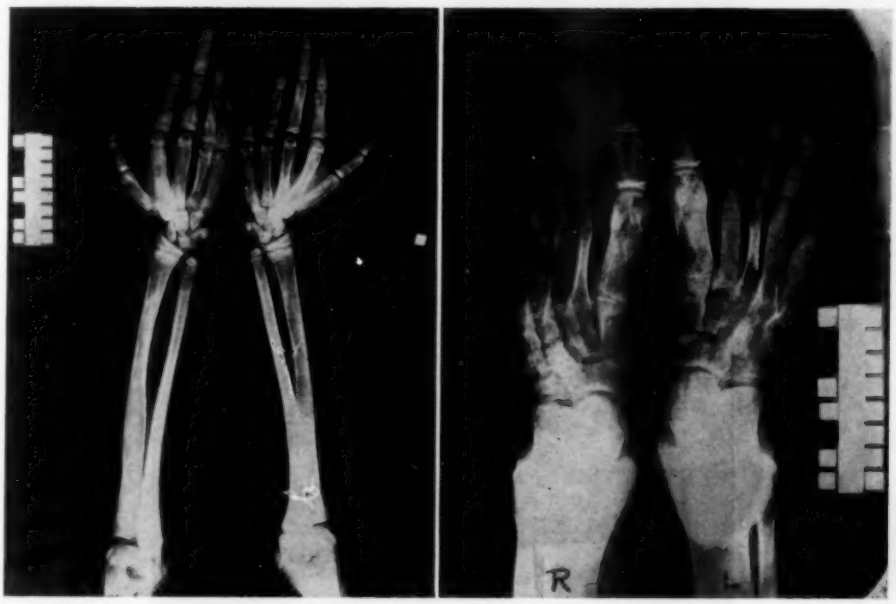


FIG. 6. (*Left*) January 10, 1945. Forearms and hands showing asymmetrical pseudocystic areas. Note absence of involvement of several small bones.
FIG. 7. (*Right*) January 10, 1945. Feet showing cystic changes which are slightly more extensive in right foot.

are non-linked in inheritance gave acceptable evidence that the twins are dizygotic. Although they both are blood type A, they differ in iris pigmentation, intelligence quotient, stature and quantitative value of finger prints. The finger prints were examined by Dr. Harold Cummins,[15] Professor of Microscopic Anatomy at Tulane Medical School, who concluded that the twins were dizygotic and also that there were no aberrant features in the patient's handprints to suggest a systemic disease.

The twin sister is a normal child and the parents reported a progressive disparity in the two children from about the age of three years (figures 9, 10, and 11). The normal twin developed more rapidly, walked and talked almost one year earlier than the patient, and made average progress in school. The patient never progressed beyond the first grade. Comparative measurements taken in April 1945 were:

	Patient	*Normal Twin*
Height	130 cm.	135 cm.
Weight	63 lb.	61 lb.
Crown	59 cm.	53 cm.

Physical examinations of the normal twin have disclosed no abnormalities. Roentgenographic examination of her entire skeleton in March 1944 gave negative findings except for spina bifida occulta of the fifth lumbar vertebra. The bone age was compatible with her chronologic age. Electroencephalogram for the twin made in October 1945 was interpreted as that of a normal 10 year old child whereas that of the patient resembled more nearly the record of a 40 year old woman. Dental examination showed that the twins have the same number of caries in the same position in the

FIG. 8. May 29, 1944. Pathological fracture of right humerus. Note cystic areas, expansion of mid-shaft and thinning of cortex.

same teeth. However, the patient's caries were definitely more advanced and this may have some relationship to her more mature degree of calcification.

Routine blood studies on the twin yielded findings within normal limits. Her blood chemistry showed:

	Calcium	*Phosphorus*	*Alkaline phosphatase*
3/28/44	——	5.0 mg./100 c.c.	6.4 Bodansky Units
4/19/45	12.4 mg./100 c.c.	4.5	7.5

A five year old niece (L–44–16104B) of the twins was admitted to Charity Hospital in January 1945 with complaints of vertigo, nystagmus and weakness. Medical investigation was non-contributory, and the patient was discharged with a diagnosis of possible brain tumor. Certain familial resemblances to our patient were noted, and it was suggested that her symptoms might be attributed to an allied con-

dition. However, physical examination, skeletal roentgenograms and blood chemical determinations for calcium, phosphorus and alkaline phosphatase were within normal limits. No additional data have yet been collected on this patient.

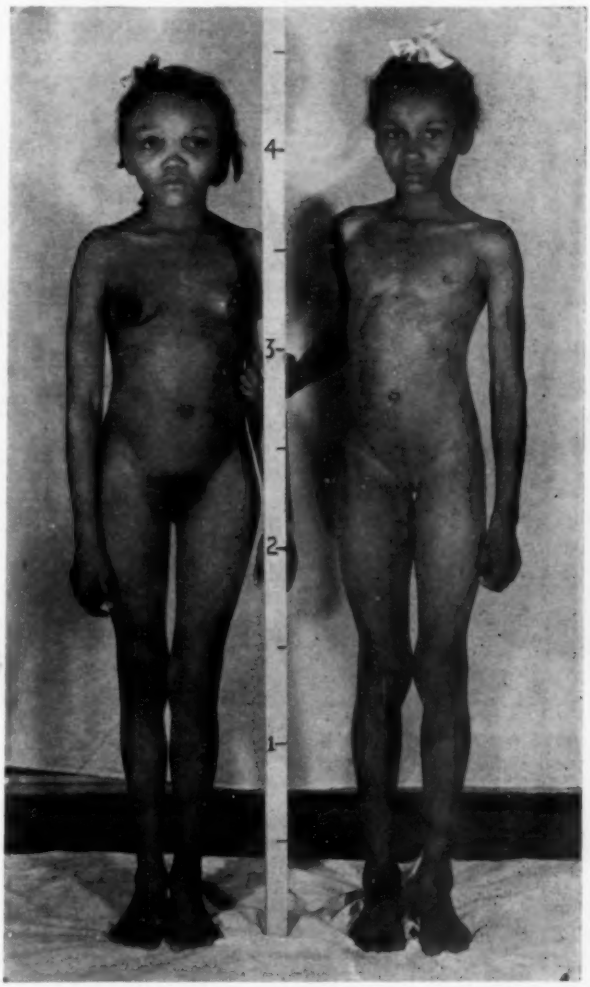


FIG. 9. April 19, 1945. Patient. Normal twin sister. Note deformity of skull, mammary development, pubic hair and body contour as compared to twin.

ETIOLOGY

Albright and his associates [2] originally suggested a neurologic or embryonic defect as the etiologic factor since the peculiar distribution of osseous and cutaneous lesions would tend to exclude primary metabolic or endocrine factors. Evidence is accumulating which supports this embryonic interpretation. Albright, Scoville and Sulkowitch [16] in 1938 described the occurrence of the syndrome in a 21 year old man who showed neurologic changes in reflexes and in sensation in relation to the pigmented skin lesions. They also cited the work of

Ford and Guild,[17] who observed sexual precocity following injuries, infections and pineal tumors involving the region of the hypothalamus.

Freedman [18] described the clinical features of this syndrome in 1932 under the title of "Disturbance of the Function of the Suprarenal Glands." This patient was later included as case No. 3 in Albright's paper in 1937 and subse-

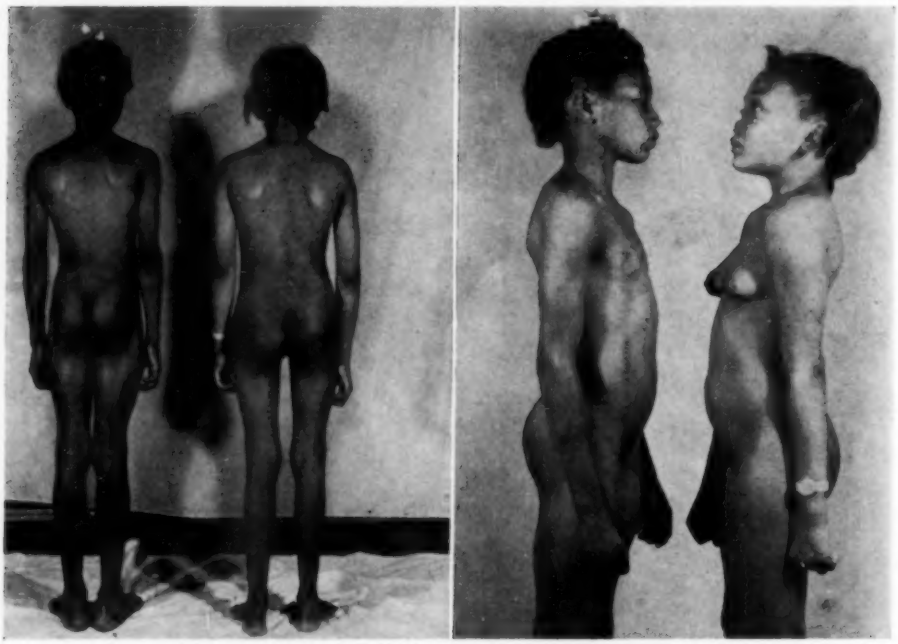


FIG. 10. (*Left*) Same. Note broad hips of patient and pigmented areas over spinal column and in gluteal region.
FIG. 11. (*Right*) Same.

quently came to autopsy. Dr. H. E. MacMahon,[19] Professor of Pathology at Tufts College Medical School, who studied the postmortem material, kindly wrote us concerning his findings. In respect to the central nervous system he noted "many anomalies of the brain and included among these was an alteration involving the hypothalamic nuclei along one side. It gave the appearance of an accessory nucleus with well formed nerve cells and axones, though it could equally well have been an asymmetrical division of one of the ganglia in which one portion appearing as an accessory nucleus lay in very close apposition to one of the nuclei normally found." Dr. MacMahon expects to report this case soon.

DISCUSSION

The most striking features of the case reported are the obvious endocrine dysfunction, the generalized but asymmetrical skeletal involvement, the premature physical development and epiphyseal closure, and the patchy skin pigmentation which has little apparent relation to the skeletal lesions. There is no evidence to support the assumption that heredity, environment or infection are

etiologic factors. Albright's hypothesis that this is a neurologic defect in the region of the hypothalamus on an embryonic basis seemingly is the most logical starting point for any attempt to explain and correlate our observations.

Continued study of this case may reveal many valuable clues concerning the nature and course of this unusual condition. Of particular interest are:

1. A check on the urinary excretory rates of pituitary gonadotropins, estrogens and 17-ketosteroids to see if they are proportionate to the degree of maturation rather than to the chronologic age.
2. Will progestin induce menstruation, that is, is the follicle-stimulating hormone secreted by the anterior pituitary but not the luteinizing hormone?
3. Will the condition become stationary after epiphyseal union?
4. Will malignant degeneration occur? Coley and Stewart [20] recently reported bone sarcoma developing in two cases of polyostotic fibrous dysplasia. They described essentially identical histologic patterns of pleomorphic spindle and giant cell sarcomata for both cases. Each case showed evidence of metastasis and also had an unusual response to radiotherapy.
5. What will be the effect and action of aluminum acetate on the bone lesions?

Summary

A patient with polyostotic fibrous dysplasia examined over a period of 20 months has shown some clinical maturation but little physiologic change in that period. This case is unusual because the patient was a negro and had a normal dizygotic twin. Diagnosis is based on widespread but asymmetrical fibrous dysplasia of the skeleton, precocious puberty, patchy pigmentation of the skin, and repeatedly normal values of blood calcium and phosphorus although alkaline phosphatase was consistently elevated. A primary germ plasm defect is the most plausible etiologic hypothesis. Continued study of this case may contribute to our knowledge of this unusual entity.

Note: The authors wish to express their sincere appreciation to Granville A. Bennett, M.D., Professor of Pathology at the University of Illinois College of Medicine, for stimulating interest in this case and for preparing and examining the biopsied material; to Charles E. Dunlap, M.D., Professor of Pathology at Tulane University Medical School; Fuller Albright, M. D., Assistant Professor of Medicine, Harvard Medical School; H. E. MacMahon, M.D., Professor of Pathology and Bacteriology, Tufts College Medical School; Harold Cummins, Ph.D., Professor of Microscopic Anatomy, Tulane University Medical School; Josephine E. Ferguson, Medical Social Service Department, Charity Hospital, and to the various services at Charity Hospital for their aid and constructive criticisms. The photomicrograph was made by Dr. Dunlap. Miss Vera Morel and Mr. Meade of the Art Department at Tulane University Medical School supplied the diagram and the photographs respectively.

BIBLIOGRAPHY

1. Mandl, F.: Therapeutischer Versuch bei Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors, Wien. klin. Wchnschr., 1925, xxxviii, 1343.
2. Albright, F., Butler, A. M., Hampton, A. O., and Smith, P.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females; report of 5 cases, New England Jr. Med., 1937, ccxvi, 727–746.

3. GORHAM, L. W., and others: Albright's syndrome; group of cases characterized by osteitis fibrosa disseminata, areas of pigmentation and gonadal dysfunction, Clinics, 1942, i, 358–385.
4. WEIL: Pubertas praecox und Knochenbrüchigkeit, Klin. Wchnschr., 1922, i, 2114.
5. PRIESEL, R., and WAGNER, R.: Ostitis fibrosa cystica generalisata (Osteodystrophia fibrosa), Ztschr. f. Kinderh., 1932, liii, 146–161.
6. SNAPPER, I., and PARISEL, C.: Generalized xanthomatosis of bones (confusion with Recklinghausen's disease), Maandschr. v. kindergeneesk., 1933, ii, 359–377.
7. HUMMEL, R.: Zwei Fälle von Ostitis deformans Paget juvenilis, Röntgenpraxis, 1934, vi, 513–519.
8. PAGNIEZ, P., PLICHET, A., and FAUVET, J.: Un cas d'ostéite fibro-kystique de localisation et d'evolution anormales, Bull. et mém. Soc. méd. d. hôp. de Paris, 1938, liv, 733–736.
9. ALBRIGHT, F.: Personal communication.
10a. LICHTENSTEIN, L.: Polyostotic fibrous dysplasia, Arch. Surg., 1938, xxxvi, 874–878.
10b. LICHTENSTEIN, L., and JAFFE, H. L.: Fibrous dysplasia of bone, Arch. Path., 1942, xxxiii, 777–816.
11. BENNETT, G. A.: Personal communication.
12. DUNLAP, C. E.: Personal communication.
13. HELFET, A. J.: New concepts of parathyroid function and its clinical application; preliminary report on results of treatment of generalized fibrocystic and allied bone diseases and of rheumatoid arthritis by aluminum acetate, Brit. Jr. Surg., 1940, xxvii, 651–677.
14. GHORMLEY, R. K., and HINCHEY, J. J.: Use of aluminum acetate in the treatment of malacic diseases of bone, Jr. Bone and Joint Surg., 1944, xxvi, 811–817.
15. CUMMINS, H.: Personal communication.
16. ALBRIGHT, F., SCOVILLE, W. B., and SULKOWITCH, H. W.: Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation, and gonadal dysfunction; further observations including report of 2 more cases, Endocrinology, 1938, xxii, 411–421.
17. FORD, F. R., and GUILD, H.: Precocious puberty following measles encephalomyelitis and epidemic encephalitis, with discussion of relation of intracranial tumors and inflammatory processes to syndrome of macrogenitosomia praecox, Bull. Johns Hopkins Hosp., 1937, lx, 192–203.
18. FREEDMAN, H. J.: Disturbances of function of suprarenal glands in children, Am. Jr. Dis. Child., 1932, xliv, 1285–1292.
19. MACMAHON, H. E.: Personal communication.
20. COLEY, B. L., and STEWART, F. W.: Bone sarcoma in polyostotic fibrous dysplasia, Ann. Surg., 1945, cxxi, 872–881.

HEART TRAUMA: MYOCARDIAL INVOLVEMENT (CONTUSION) FOLLOWING A NON-PENETRATING INJURY TO THE CHEST (AIRPLANE ACCIDENT) *

By HANS H. HECHT, M.D., *Salt Lake City, Utah*

A NUMBER of recent reviews have pointed to the apparent frequency with which non-penetrating injuries to the chest are complicated by lesions of the heart.[1-6] In most of the earlier reports the injury to the heart was striking, im-

* Received for publication April 4, 1946.
From the Department of Medicine, University of Utah Medical School, Salt Lake City, Utah. The case was observed on the wards of the Wm. J. Seymour Hospital, Eloise, Michigan.

mediate, and either fatal or incapacitating. In others severe cardiac failure, conduction disturbances or rupture of the myocardium occurred after a relatively silent period.† The subject has become increasingly important from the standpoint of industrial [5, 8, 9, 10, 11] and military [3, 4, 12–15] compensation. The use of early and repeated electrocardiographic examinations has been stressed as being necessary in the presence of any injury to the chest, as it has become apparent that cardiac involvement may occur with little or no other evidence to indicate its existence. However, very few attempts have been made to interpret the electrocardiographic findings obtained or to recognize in reporting the electrocardiographic abnormalities in cases of this type that extensive aberrations of a presumably "normal" pattern may occur in otherwise healthy individuals.[16, 17]

The following example is described because it represents a type of injury hitherto not reported as a cause of traumatic heart disease. It is likely, however, that proper examination will reveal a high incidence of myocardial involvement in accidents of this type.

Furthermore, the example illustrates that careful clinical observation with frequent electrocardiograms including a number of precordial leads may reveal temporary involvement of the heart muscle which would be easily missed on a routine accident service.

Case Report

The accident involved a 34 year old American civilian air pilot and engine instructor who had always been in excellent health and had successfully passed an army examination for air cadet rating three weeks before. On June 6, 1943, during a routine flight in a three seater open cockpit plane the engine stalled at 400 feet. He crash-landed in a marshy clearing, the plane nosed over and the patient was violently yanked forward into his safety-belt. When admitted to the hospital two hours later he was found to be in shock with evidence of severe crushing injuries to the left lower chest, left upper abdomen and to the back. Roentgenograms revealed fractures of the left fifth and sixth ribs and of the right sixth and tenth ribs. There was a fracture of the sacrum with extension into the iliac crest, a fracture of the transverse processes of the fifth lumbar vertebra and comminuted fractures of the right radius and ulna and of the left tibia and fibula. There was a small collection of fluid in both pleural cavities. The patient responded well to treatment and received a total of 500 ml of plasma, 500 ml of whole blood and 2000 ml of 5 per cent glucose in saline solution during the first 24 hours. A complete physical examination performed on the morning of the first hospital day was normal except for a few scattered râles in both lung fields and the injuries noted above. The blood pressure had risen from the admitting level of 90 mm. of mercury systolic and 60 diastolic to 110 systolic and 70 diastolic. The heart sounds were forceful and of equal intensity over the base, and no enlargement and no murmurs were noted. The rhythm was regular but rapid (130 beats per minute). On the evening of the first day (24 hours after the injury) the patient received 10 ml of adrenal cortical extract intramuscularly. Two hours later the patient was found to be in acute distress; he was intensely cyanotic, severely dyspneic and perspired profusely. The heart sounds appeared muffled and the pulse rate had risen to 145 beats per minute. The lungs

† Joachim and Mays [7] noted a ventricular aneurysm 12 years after a chest injury in a 24 year old man. A similar instance was reported by Hildebrandt (E. Warburg l.c.), in which a ventricular aneurysm was present in a 27 year old individual 18 years after injury. No other cause for the aneurysm was found in either case. Compensation was granted to a man who suffered incapacitating attacks of the Adams-Stokes variety with complete a.v.-block beginning nine months after a chest injury.[8]

were not examined at this time. The patient was immediately given oxygen and received 0.5 gm. aminophyllin and 2 ml salyrgan intravenously. Within the next hour he began to improve and by midnight had all but completely recovered from this episode. A lumbar puncture during this time revealed normal findings. When seen the following morning by a medical consultant the patient appeared comfortable and was breathing normally. The heart was found to be slightly enlarged although the patient's stocky build made a proper evaluation of the heart size difficult. A per-

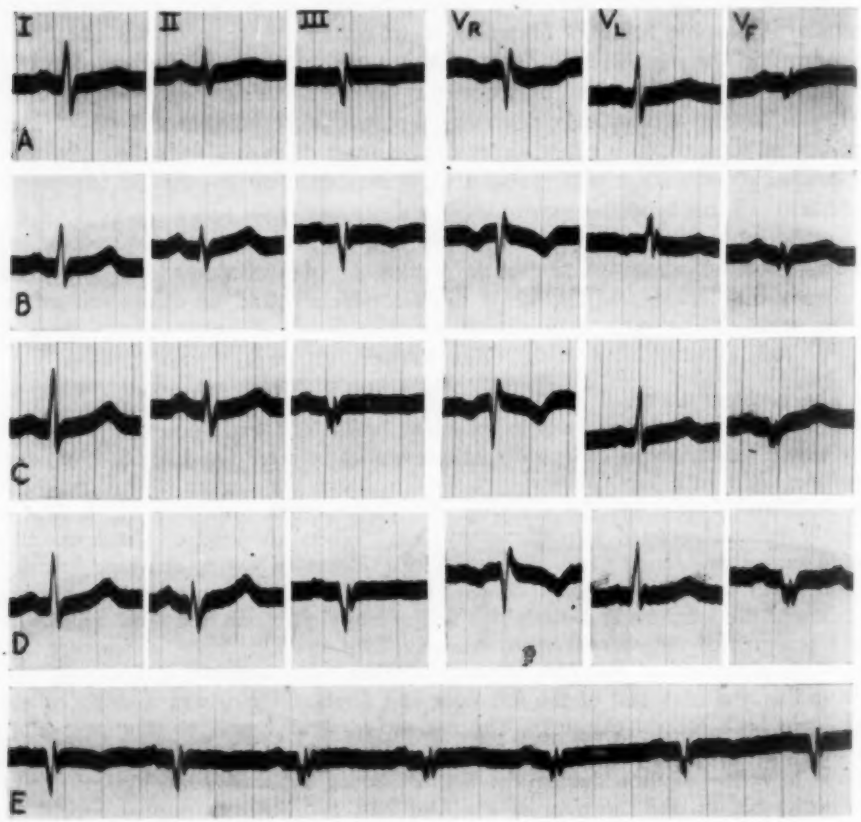


FIG. 1. Standard limb leads and unipolar limb leads (extremity potentials) of right arm (V_R), left arm (V_L) and left leg (V_F). (A) 6.14, (B) 6.18, (C) 6.23, (D) 12.4.1943, (E) 6.18.1943: Lead III during forced respiration. No striking changes were noted in any of the leads illustrated or in others taken during the same period.

sistent tachycardia (130 per minute) in the face of a now almost normal temperature was noted and a diastolic gallop rhythm was distinctly audible over the apex. There were no râles in the chest. No specific therapy was instituted, but from the findings an injury to the heart muscle was suspected. This appeared even more likely from the fact that the gallop rhythm persisted until the fifth hospital day and that the pulse rate remained elevated (above 100 beats per minute) until the eleventh hospital day. The patient made a gradual and uneventful recovery. He was discharged 20 days after his accident, and when seen six months later was quite well except for a non-union of the left wrist following the fracture.

The first electrocardiogram was taken on the fourth hospital day (June 11, 1943). The three standard limb leads recorded at this time were similar in all respects to those recorded at later dates (figure 1). They always revealed left axis deviation of QRS and of T with definite Q waves in Lead III. The configuration of QRS was observed to change considerably during respiration (figure 1 E).

The tracings mounted on the right hand side of figure 1 are the so-called unipolar limb leads (extremity potentials). In recording these one of the electrodes is placed in rotation on the right arm (V_R), left arm (V_L), or the left leg (V_F). The other electrode is connected to a neutral or ground connection, the central terminal. It

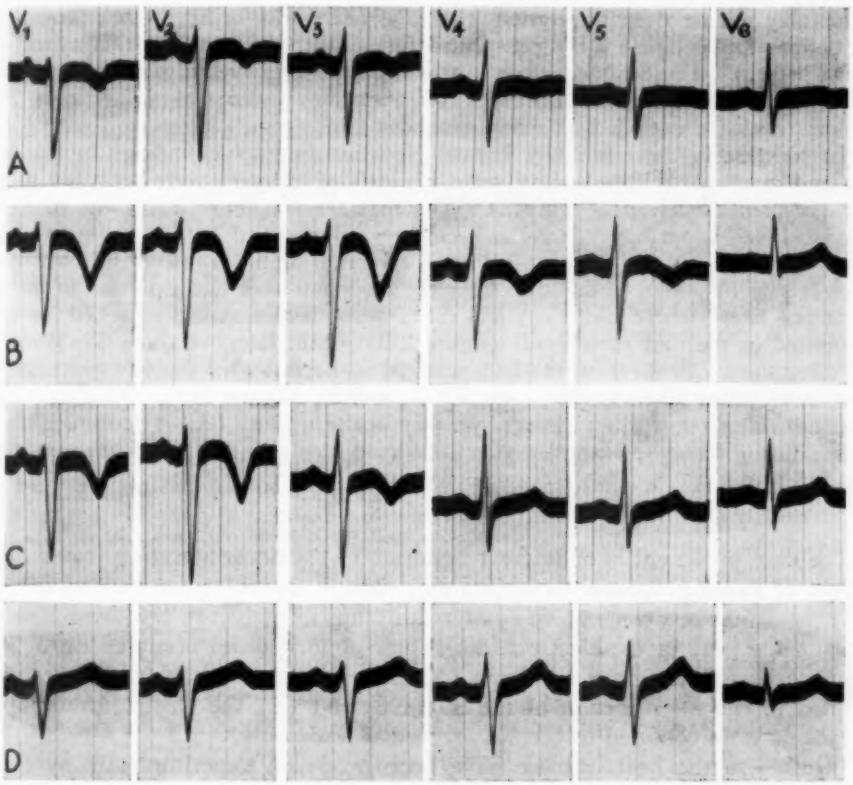


FIG. 2. Serial precordial leads: V_1 at fourth intercostal space, right sternal border, V_2 at fourth intercostal space left sternal border, V_3 half way between V_2 and V_4, V_4 at fifth intercostal space left midclavicular line, V_5 on horizontal level with Lead V_4 but in anterior axillary line, V_6 as V_5 but in left midaxillary line. (A) to (D) as in figure 1.

has been shown that the central terminal is practically void of variations in electrical potentials during the cardiac cycle [18] and consequently by using such an arrangement a record is obtained which represents the potential variations under one electrode only, in this case under the electrode placed in rotation on the extremities. Standard limb leads are records representing the summation of the variations in electrical potentials of two extremities and consequently each unipolar limb lead represents one half of a standard lead. With minor variations these unipolar limb leads had changed but little: the right arm lead (V_R) showed inversion of all electrocardiographic components, which is the rule in a normally activated heart. The left arm (V_L)

revealed large R waves at all times and the left leg (V_F) invariably showed small primary downward directed QRS complexes. This pattern is indicative of a horizontally placed heart.[19] Standard Lead III is expressed as the sum of the potentials of the left leg minus those of the left arm (V_F–V_L). This means that the large R waves present in V_L must be subtracted from the potentials of V_F. This will result in either deep Q waves or deep S waves in Lead III. The presence of deep Q waves in Lead III in the tracing obtained must therefore be considered as a result of the horizontal position of the patient's heart within the chest and cannot be considered an abnormal finding. Esophageal leads were taken on one occasion and revealed a normal pattern. The fact that the complexes in Lead III could be altered considerably during deep inspiration when the heart was being rotated around its longitudinal axis (figure 1 E) constitutes further proof for the normality of the pattern present. These findings are stressed because Q waves of the type recorded are invariably observed in instances of posterior myocardial infarction. This diagnosis could be excluded on many grounds.

In contrast to the essentially normal electrocardiographic findings in standard leads and in unipolar limb leads (figure 1), striking changes were recorded in the usual six precordial leads (figure 2). The first series (figure 2 A) was taken on June 14, 1943—seven days after the accident—and revealed flat T waves over the left ventricle (V_4, V_5, V_6) and a terminal inversion of the T waves in leads from the right side (V_1–V_3). Four days later the inversion of T had extended to include all but one lateral chest lead (V_6) and the T wave inversion had now become very pronounced in the first three leads (figure 2 B). Still later, on June 23, 1945—16 days after the accident—T waves had returned to normal over the left ventricle but still showed sharp inversion in Leads V_1, V_2 and V_3 (figure 2 D). Tracings taken six months later revealed an essentially normal pattern in all leads (figure 2 E). At no time during the episode were changes observed involving the QRS complex or the RST junction.

Discussion

The case presented is of interest because: (1) a nonpenetrating trauma was capable of causing apparently substantial though transient myocardial injury; (2) myocardial involvement was not readily apparent before the third hospital day, and the peak of the electrocardiographic abnormalities occurred during the second week following the accident; (3) the electrocardiographic changes were confined to the final portion of the T wave; and (4) the electrocardiographic alterations were confined to certain precordial leads only.

Injuries to the heart muscle have been produced experimentally by direct blows to the heart muscle[20] or to the chest wall[22, 23] and in man apparently result from simple transmission of the traumatic force in a resilient and flexible thoracic cage.[1, 4, 12] Barring immediate rupture of the heart with sudden death, the myocardium may be involved in one of three ways. First, an endocardial tear may penetrate into the myocardium. In instances of this type partial rupture of the myocardium may become complete and sudden death may occur following a latent interval.[1, 3, 6, 7, 10] In other cases the injury may result in bruises to the myocardium consisting of extravasation of blood into the myocardium with rupture of myocardial fibers, secondary leukocytic infiltration, edema, resolution and finally scar tissue formation.[1, 13, 19–25] Such lesions usually spread from the epicardial surface inward. Hemopericardium, myocardial scarring with aneurysm of the type mentioned above or even rupture may result[26] although complete functional recovery with dense scar formation appears to be

more common. The third type consists of direct injury to the coronary arteries and results in secondary myocardial infarction. True examples of this type are not common, and many reports of "traumatic" coronary occlusion such as those reported by Leinoff, Lee and Boas [9, 14, 27] may be re-interpreted as instances of contusion or primary scarring of the heart muscle. That intimal hemorrhage into a previously atheromatous coronary artery may follow external violence and result in the typical clinical syndrome appears logical, however, and is attested to in a number of reports [3b, 4, 9a, 27-32] though repeatedly challenged by Master and his associates.[33] Even an apparently normal coronary system may be damaged to an extent resulting in occlusive thrombus formation.[34]

In the present case the injury was severe enough to cause an episode of left ventricular failure with a paroxysm of dyspnea 24 hours after the injury and to produce a persistent gallop rhythm during the first week. That this was apparently the result of a myocardial contusion involving epicardial layers but not penetrating deeply can be clearly argued from the characteristic electrocardiograms obtained. The latent period before the inversion of T makes its appearance has been observed by others. This delay is comparable to that of the T wave inversion associated with myocardial infarction secondary to coronary occlusion. Here T wave changes also occur late, in contrast to the almost immediate changes of QRS and of the RST-junction, and they appear most pronounced at a time when regenerative processes in the infarcted area are at their height. Injuries of the kind discussed are grossly and histologically similar to those produced by acute occlusion of a coronary artery [13, 20, 34, 25] with the exception that the latter usually involves a greater area and as a rule traverses almost the entire thickness of cardiac muscle. This penetrance of myocardial infarctions accounts for the frequency with which alterations of the QRS complexes are encountered. Deeply penetrating myocardial infarcts cause a decrease in R and the appearance of deep Q waves due to the escape of primarily negative potentials of the ventricular cavities through the electrically inert infarcted muscular wall to the surface and thence to the periphery.[35] In the case presented enough healthy and active muscle must have been present underneath the lesion to prevent such changes from occurring. Infarcts imbedded in layers of relatively normal muscle tissue are occasionally observed presenting only T wave changes.[19] A limited destruction of this type closely resembles the hemorrhagic areas experimentally produced or actually encountered in myocardial contusions.[1, 6, 13, 20-25] The absence of changes of QRS complex in this case and in those reported by others is then compatible with the superficiality of the lesion. This could be either endocardial or epicardial. An endocardial tear would be expected to result in QRS changes of the vibratory type and in little if any alteration of T. The characteristic pattern of subendocardial necrosis as described by others [36] was absent. It appears from experimental studies and from autopsy examinations that the typical myocardial contusion involves the epicardial muscle layers and in that respect can be compared with the changes of the heart muscle associated with pericarditis. One might effectively argue that many of the electrocardiographic findings on record and those reported in the case presented were of the type suggesting pericarditis. Pericardial involvement is indeed common in nonpenetrating chest injuries.[37] In Warburg's series [3] pericarditis was clinically suspected in 30 and was found in 15 of 60 cases which came to autopsy (25 per

cent). The electrocardiographic changes in direct lacerating wounds of the heart are likewise often dominated by those ascribable to an accompanying pericarditis.[38-40] As the electrocardiographic changes of pericarditis are due to involvement of superficial myocardial layers,[41] the differentiation between electrocardiographic changes of "traumatic" pericarditis and those produced by direct bruising of the myocardium becomes immaterial. The tracing which was recorded was one which presented the typical picture of lesions of the epicardial muscle layers. The use of multiple precordial leads gives further clues as to the exact location of the epicardial injury. Chest leads V_1, V_2 and V_3—leads close to the sternum—were primarily affected, suggesting that the lesion faced straight anteriorly, involving the surface of the right and left ventricles but not involving the apical region. Such an "antero-septal" location is not deflected to the extremities [19] and consequently escapes detection by the conventional methods.

Not only the location but also the degree of involvement can be estimated from the electrocardiographic pattern. No striking upward displacement of the RST junction was observed. If present, it is associated with acute severe injury to the heart muscle. It is unlikely that RST displacement was present but escaped detection, because the gradual waxing and waning of the changes seen in figure 2 permits the assumption that alterations of the ventricular complexes began at or very shortly before the time the first tracing was recorded. T wave changes of the kind presented and without striking elevation of the RST-junction are seen at marginal regions of experimental infarctions where collateral circulation is active and where the injury set by the arterial occlusion is least pronounced.[36] It appears from recent observations that T wave inversion may precede ST displacement as an early sign in the event of progressive myocardial ischemia.[42] It has been shown that terminal T wave inversion was the first change to occur when a coronary artery of a dog was clamped for a short period of time. A more prolonged clamping caused ST displacement and finally QRS changes of the classical pattern were produced. The absence of RST displacement in the records obtained from this patient must indicate a relatively mild injury, an assumption which is well supported by the gradual disappearance of all clinical and electrocardiographic signs.

In conclusion the injury observed must have been mild and superficial. It involved the epicardial layers of heart muscle of the anterior surface and did not extend to the apical region. The changes were not evident in any of the standard limb leads and extremity potentials. A routine chest lead (IVF) would have given little additional information. The gradual appearance, extension and involution of the lesion seen in precordial leads fulfilled the prophecy of White and Glendy that "the electrocardiogram will become a very important aid in the estimation of the amount of damage both structural and functional which the heart muscle suffers as the result of the injury." [43]

Summary

1. A severe nonpenetrating injury to the chest resulted in transient myocardial injury as evidenced by:

a. Onset of left ventricular failure 24 hours after injury.
b. Persistent tachycardia and gallop rhythm during the first week following the injury.
c. Progressive electrocardiographic changes from the first to the third week after the accident.

2. The resulting lesion was judged to be superficial because of the absence of demonstrable ST displacement. It was thought to be epicardial because the electrocardiographic pattern obtained was similar in many respects to the changes observed in certain stages of pericarditis.

3. The location of the lesion made its detection possible only by the use of multiple precordial leads. These, in addition, allowed some insight into the progression, extension and involution of the process.

BIBLIOGRAPHY

1. Bright, E. F., and Beck, C. S.: Non-penetrating wounds of the heart, Am. Heart Jr., 1935, x, 293.
2. Barber, H.: Trauma of the heart, Brit. Med. Jr., 1938, i, 433.
3a. Warburg, E.: Subacute and chronic pericardial and myocardial lesions due to non-penetrating traumatic injuries, 1938, Oxford University Press, London.
b. Warburg, E.: Myocardial and pericardial lesions due to non-penetrating injury, Brit. Heart Jr., 1940, ii, 271.
4a. Sigler, L. H.: Trauma of the heart due to nonpenetrating chest injuries, Jr. Am. Med. Assoc., 1942, cxix, 855.
b. Sigler, L. H.: Traumatic injury of the heart, Am. Heart Jr., 1945, xxx, 459.
5. Ahrenberg, H.: Traumatic heart disease: a clinical study of 250 cases of nonpenetrating chest injuries and their relation to cardiac disability, Ann. Int. Med., 1943, xix, 326.
6. Barber, H.: The effects of trauma, direct and indirect, on the heart, Quart. Jr. Med., 1944, xiii, 137.
7. Joachim, H., and Mays, A. T.: A case of cardiac aneurysm probably of traumatic origin, Am. Heart Jr., 1926–27, ii, 682.
8. Kessler, H. H.: Accidental injuries, 2nd ed., 1941, Lea and Febiger, Philadelphia.
9a. Leinoff, H. D.: Direct nonpenetrating injuries of the heart, Ann. Int. Med., 1940, xiv, 653.
b. Leinoff, H. D.: Acute coronary thrombosis in industry, Arch. Int. Med., 1942, lxx, 33.
10. Foster, R. F.: The relation of trauma to heart disease, Indust. Med., 1938, vii, 258.
11. Anderson, R. G.: Nonpenetrating injuries of the heart, Brit. Med. Jr., 1940, ii, 307.
12. Foresee, J. A., Shefts, L. M., Burbank, B., Fitzpatrick, L. J., and Burford, Th. H.: The management of thoracic war injuries, Jr. Lab. and Clin. Med., 1943, xxviii, 418.
13. Wilson, J. V.: The pathology of closed injuries of the chest, Brit. Med. Jr., 1943, i, 470.
14. Lee, R. V., Ussher, N. T., and Houch, G. H.: Acute traumatic heart disease, Am. Jr. Med. Sci., 1943, ccvi, 722.
15. Leavell, B. S.: Acute heart failure following blast injuries, War Med., 1945, vii, 162.
16. Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D.: The effects of exercise and of four commonly used drugs on the normal human electrocardiogram, with particular reference to T wave changes, Jr. Clin. Invest., 1942, xxi, 409.
17. White, P. D., Chamberlain, F. L., and Graybiel, A.: Inversion of the T waves in Lead II caused by a variation in the position of the heart, Brit. Heart Jr., 1941, iii, 233.
18. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms that represent the potential variations of a single electrode, Am. Heart Jr., 1934, ix, 447.
19. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The precordial electrocardiogram, Am. Heart Jr., 1944, xxvii, 19.
20. Moritz, A. R., and Atkins, J. P.: Cardiac contusion, Arch. Path., 1938, xxv, 445.
21. Boyd, L. J., and Scherf, D.: El electrocardiograma en las injurias epicárdicas, endocárdicas (y miocárdicas subyacentes) localizadas, Rev. argent. de cardiol., 1940, vii, 1.
22. Schlomka, G.: Commotio cordis und ihre Folgen, Ergebn. d. inn. Med. u. Kinderh., 1934, xlvii, 1.

23. Kissane, R. W., Fidler, R. S., and Koons, R. A.: Electrocardiographic changes following external chest injuries to dogs, Ann. Int. Med., 1937, xi, 907.
24. Scherf, D., and Terranova, R.: Estudio electrocardiográfico de las desviaciones del segmento ST en las contusiones torácicas experimentales, Rev. argent. de cardiol., 1942, ix, 157.
25. Forero, A., Silva, B., and Saffie, F.: Estudio electrocardiografico y anatomico del traumatismo precordial experimental, Rev. argent. de cardiol., 1944, xi, 77.
26. Krumbhaar, E. B., and Crowell, C.: Spontaneous rupture of the heart, Am. Jr. Med. Sci., 1925 clxx, 828.
27. Boas, E. P.: Angina pectoris and cardiac infarction from trauma or unusual effort, Jr. Am. Med. Assoc., 1939, cxii, 1887.
28. Schmincke, A.: Beitrag zur traumatischen Aetiologie der Arteriosklerose, Deutsch. Arch. f. klin. Med., 1925, cxlix, 145.
29. Kienle, F.: Klinische und electrokardiographische Beobachtungen bei traumatischem Hinterwand Infarkt, Ztschr. f. Kreislaufforsch., 1938, xxx, 674.
30. Boas, E. P.: Some immediate causes of cardiac infarction, Am. Heart Jr., 1942, xxiii, 1.
31. Jekl, E., and Greenstein, J.: Fatal coronary sclerosis in a boy of 10 years, Lancet, 1944, ii, 5, 659.
32. Wearn, J. T., in discussion to Beck, C. S.: Contusion of the heart, Jr. Am. Med. Assoc., 1935, civ, 114.
33a. Master, A. M., Dack, S., and Jaffe, H. L.: Activities associated with the onset of acute coronary artery occlusion, Am. Heart Jr., 1939, xviii, 434.
b. Master, A. M.: Letter to the editor, Jr. Am. Med. Assoc., 1942, cxx, 392.
c. Master, A. M.: Letter to the editor, Jr. Am. Med. Assoc., 1945, cxxix, 90.
34. Viko, L. E.: Personal communication: a 38 year old man was hit by a golf ball over the lower part of the sternum and died 3 days later with signs and symptoms of recent coronary occlusion. A fresh thrombus was found in the anterior descending branch of the left coronary artery. There was no evidence of atheromatous changes in any other vessel examined. See also a similar case, often cited: Queries and Minor Notes, Jr. Am. Med. Assoc., 1933, ci, 1503.
35. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The form of the electrocardiogram in experimental myocardial infarction. III. The later effects produced by ligation of the anterior descending branch of the left coronary artery, Am. Heart Jr., 1935, x, 903.
36. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: The form of the electrocardiogram in experimental myocardial infarction. IV. Additional observations on the later effects produced by ligation of the anterior descending branch of the left coronary artery, Am. Heart Jr., 1935, x, 1025.
37. Barber, H.: Electrocardiographic changes due to trauma, Brit. Heart Jr., 1942, iv, 83.
38. Davenport, G. L., and Markle, P.: The electrocardiogram in stabwounds of the heart, Jr. Thorac. Surg., 1933–34, ii, 376.
39. Noth, P. H.: Electrocardiographic patterns in penetrating wounds of the heart, Proc. Am. Fed. Clin. Res., 1944, i, 49; Am. Heart Jr., 1946, xxxii, 713.
40. Langendorf, R., and Goldberg, S.: The electrocardiogram in traumatic pericarditis, Am. Heart Jr., 1942, xxiv, 412.
41. Burchell, H. B., Barnes, A. R., and Mann, F. C.: The electrocardiographic picture of experimental localized pericarditis, Am. Heart Jr., 1939, xviii, 133.
42. Bayley, R. H., Ladue, J. S., and York, D. J.: Electrocardiographic changes (local ventricular ischemia and injury) produced in the dog by temporary occlusion of a coronary artery showing a new stage in the evolution of myocardial infarction, Am. Heart Jr., 1944, xxvii, 164.
43. White, P. D., and Glendy, R. E., *in* Brahdy, L., and Kahn, S.: Trauma and disease, 1937, Lea and Febiger, Philadelphia.

OXYGEN INHALATION IN THE TREATMENT OF SPONTANEOUS PNEUMOTHORAX *

By EDWARD PRESS, Major, M.C., A.U.S., *Englishtown, New Jersey*

SO-CALLED benign, idiopathic, spontaneous pneumothorax has been recognized more and more frequently during the past two or three decades. Inasmuch as this is chiefly an illness of apparently healthy, young males, it is not infrequent in the armed forces. In 1943, there were 873 hospital admissions with a primary diagnosis of spontaneous pneumothorax in the Army in the continental United States.[1] The treatment in common usage consists of bed rest and mild sedation. The average length of hospitalization in the army cases quoted above was 40 days per person.

In addition to the above conservative treatment, other methods have been advocated to hasten reëxpansion. Waring [2] recommended injection of a sterile, irritant solution into the pleural cavity to promote adhesions between the parietal and visceral pleura. Welkind and Herman,[3] working chiefly on tuberculous patients with induced pneumothorax, have shown that lavage of the pleural cavity with 100 per cent oxygen considerably hastens reëxpansion. From this, they recommend its use in spontaneous pneumothorax and describe one case in which it was used successfully after air aspiration was unsuccessful. Aspiration of air from the pleural cavity has been used by many. Indeed, when pressure pneumothorax exists, it is indispensable and urgent. Philips and Knoepp [4] advocate injection of oxygen intrapleurally, if frequent withdrawal of air is not successful.

Until recently, rupture of a subpleural bleb was believed by many authorities to be the most frequent cause of spontaneous pneumothorax. However, the very thorough studies of Macklin and Macklin [5] suggest pulmonic interstitial emphysema as the etiologic agent in many cases.

Fine, et al.[6] published a description of the inhalation of 95 per cent oxygen to reduce gaseous, intestinal distention. Since then, others have found this method effective. It has also been used to hasten absorption of retained air (chiefly nitrogen) from the cerebrospinal space following pneumoencephalography,[7] and from subcutaneous tissues in subcutaneous emphysema. The principle involved is simply that when blood with the customary small amount of nitrogen in physical solution, comes in contact with an inspired gas that has no nitrogen in it (100 per cent oxygen), rather than with air containing the usual 80 per cent nitrogen, it will give off most of its nitrogen. As the retained gas is chiefly nitrogen, in a relatively short time this is all dissolved into the blood and then given off in the alveolar air, which is almost entirely oxygen.

This rationale suggested itself to the author for application in spontaneous pneumothorax, and its use apparently hastened reëxpansion considerably. However, only a single case was available and no conclusions can be drawn. Nevertheless, as this illness is not infrequent in larger Army and Navy hospitals, and since it seems to save many hospital days per patient, it is being suggested for a controlled trial to determine its merit, if any. In addition to increasing the rapidity of resorption of the pneumothorax, the inhalation of 100 per cent oxygen also relieves the apprehension, strained effortful breathing, and pain that is often present during the first day or two of the disease.

* Received for publication October 2, 1945.

Case Report

A 28 year old white, male soldier was admitted to the Army Air Forces Station Hospital at Homestead, Florida, on March 31, 1944. He complained of pain in the right shoulder and at the apex of the right lung. The pain was sharp, aggravated by deep breathing and movement of the right upper extremity, and there was an associated dyspnea. The onset was sudden, and occurred early in the morning, while still asleep. There was no previous similar episode and the personal and family history was negative for tuberculosis.

Physical examination revealed a well developed and nourished young man with only mild respiratory distress. Roentgenograms confirmed the physical signs of collapse of the right lung and revealed complete collapse of the upper and lower right lobes and about 80 per cent collapse of the middle lobe. Evidence of an old well-healed childhood tuberculosis was noted on the left. Complete blood count, urinalysis, and sedimentation rate were normal and two sputum specimens were negative for tubercle bacilli.

The patient was kept at complete bed rest and on the second hospital day inhalation of 100 per cent oxygen was started. This was given by oronasal mask (Army Air Forces type A–8B), and continuous flow was used. Oxygen was administered approximately three out of four hours during the first day or two, and then for three or four two-hour periods daily thereafter. This method of oxygen inhalation was continued for 10 days and for the following two days, the "demand" type of mask with a low pressure tank was used for 40 minutes, four or five times daily. Immediately following the administration of oxygen, the amplitude and frequency of respirations decreased, all pain disappeared and the patient felt completely at ease.

A roentgenogram, taken seven days after oxygen therapy was instituted, revealed 95 per cent expansion of the entire right lung, and when the next film was taken, four days later, expansion was complete.

A follow-up study, done 14 months after discharge from the hospital, revealed no pulmonary complication nor recurrence.

Comment

Although published references to the use of 100 per cent oxygen inhalation could not be found, Waring [8] states that: "Inhalation of 100 per cent oxygen has been used on many occasions for the treatment of spontaneous pneumothorax, especially those cases complicated by pulmonary interstitial emphysema. . . ." Lovelace [9] believes that the continuous flow type of mask is preferable to the "demand system," if the flow is kept high enough to avoid emptying the rebreathing bag on inspiration, thus avoiding undue suction. He further recommends interruption of the continuous inhalation of oxygen for five or 10 minutes every three or four hours and suggests that this be limited to a 48 hour period.

Summary

The inhalation of 100 per cent oxygen in cases of idiopathic, spontaneous pneumothorax is suggested for future controlled trial and its use in one patient is described. The probable advantages are: more rapid reëxpansion, relief of dyspnea, apprehension and chest pain, and reduction in time of hospitalization.

BIBLIOGRAPHY

1. "News and Comment": Bull. U. S. Med. Dept., 1944, lxxxii, 29.
2. Waring, James J.: Bull. Nat. Research Council, July, 1944, quoted in "News and Comment," Bull. U. S. Army Med. Dept., 1944, lxxxii, 29.

3. WELKIND, A., and HERMAN, M.: Rapid reëxpansion of lungs; pleural lavage with oxygen: further studies, Quart. Bull. Sea View Hosp., 1941, vi, 208–224.
4. PHILIPS, J. R., and KNOEPP, L. F.: Spontaneous pneumothorax, Dis. Chest, 1940, vi, 243–248.
5. MACKLIN, M. T., and MACKLIN, C. C.: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment, Medicine, 1944, xxiii, 281–359.
6. FINE, J., BANKS, B. M., SEARS, J. B., and HERMANSON, L.: Treatment of gaseous distension of intestine by inhalation of 95 per cent oxygen. Description of apparatus for clinical administration of high oxygen mixtures, Ann. Surg., 1936, ciii, 375–387.
7. SCHWAB, R. S., FINE, J., and MIXTER, W. J.: Reduction of postencephalographic symptoms by inhalation of 95 per cent oxygen, Arch. Neurol. and Psychiat., 1937, xxxvii, 1271–1282.
8. WARING, JAMES J., Denver, Colorado, Personal communication.
9. LOVELACE II, W. RANDOLPH, Col. M.C., Personal communication.

A FATAL CASE OF SCRUB TYPHUS INTRODUCED INTO THE UNITED STATES*

By ABRAHAM A. DUMANIS, Major, M.C., A.U.S., BENJAMIN A. SCHANTZ, Lt. Col., M.C., AU.S., and EMANUEL H. NICKMAN, Major, M.C., A.U.S.

THE facility and speed of air evacuation may result in the return of personnel who are in the incubation stages of tropical diseases. Medical officers, public health physicians and civilian practitioners in general are becoming increasingly conscious of the presence of protozoan and helminthic diseases among travelers who have returned to the temperate zone. This case calls attention to the need for the consideration of the scrub typhus group of rickettsial diseases in the fevers of troops who have recently returned from endemic areas.

CASE REPORT

The patient was a 32 year old pathologist who had served 25 months in the China-Burma-India Theater of Operations during which time he was frequently and closely in contact with scrub typhus, especially at the autopsy table. He was flown from the CBI Theater on August 3, 1945 for reassignment in the United States and reached this station August 11, 1945 after eight days of travel.

On leaving Karachi, India, the patient for the first time complained of headache, malaise and unwonted listlessness and apathy. As the flight continued, the headache became unrelenting, particularly over the retro-orbital region, and was associated with persistent nausea, intermittent vomiting and mental confusion. The symptoms became increasingly severe; the nausea and vomiting were so intense that the patient abstained from food and drink; the periods of mental wandering became more frequent and marked deafness and low-grade fever developed.

On arriving at this station, the Medical Officer was promptly hospitalized. The impaired bilateral auditory acuity, utter exhaustion, disorientation, perplexity, lassitude and strange euphoria were prominent. Dehydration was severe; the tongue was exceedingly dry, swollen, furrowed and dull, the lips fissured and covered with sordes,

* Received for publication January 26, 1946.
From Medical Service, Station Hospital, Camp Kilmer, N. J.

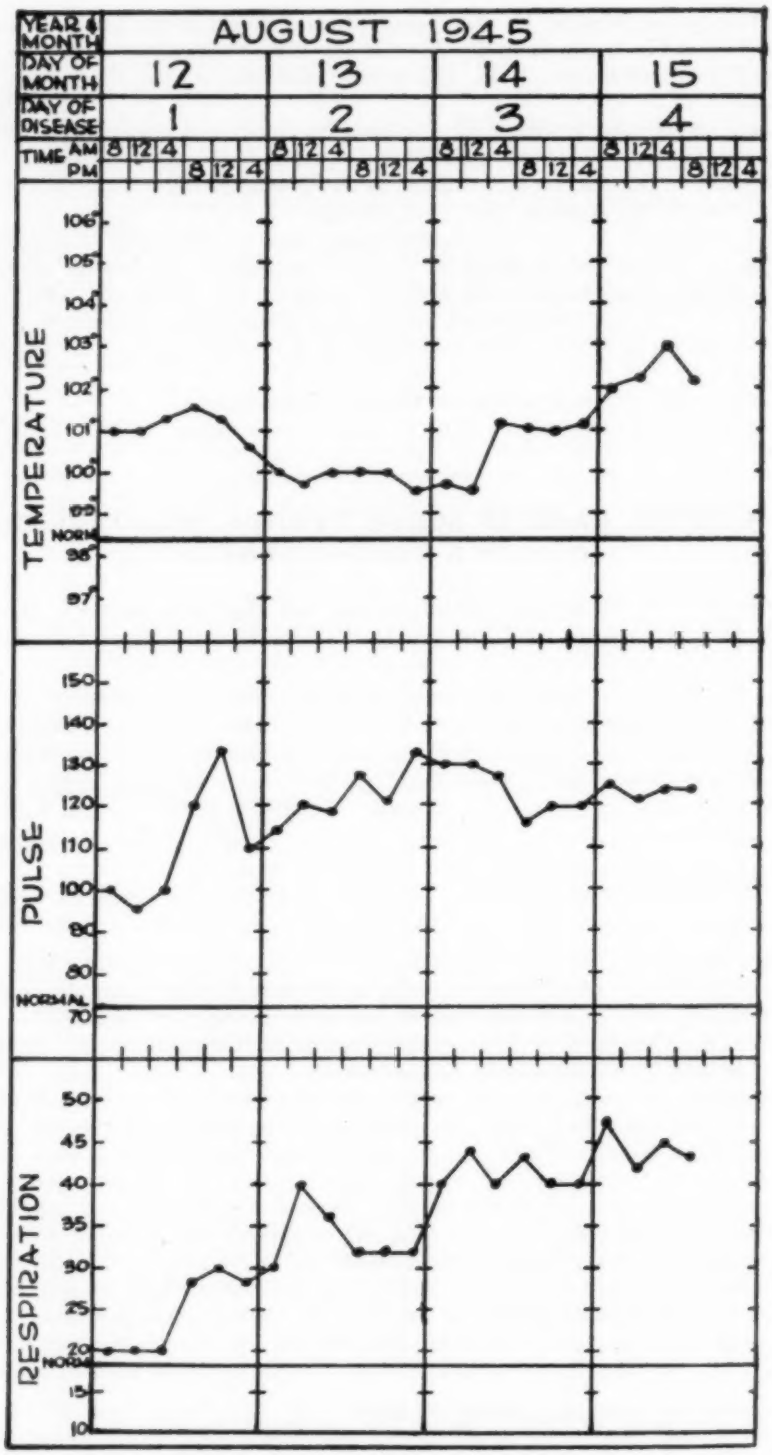


FIG. 1. Clinical course of fatal case of scrub typhus.

the skin turgor greatly diminished. The eyes revealed characteristic bilateral conjunctivitis. Respirations were rapid, 28 per minute and shallow. The lungs were normal to percussion and auscultation. The heart sounds were of poor quality and rapid, 140 per minute. Blood pressure was 102 mm. of mercury systolic and 70 mm. diastolic. A discrete pink maculo-papular eruption was present over the trunk and abdomen. Search for an eschar and regional adenopathy was negative. The liver and spleen were not palpable.

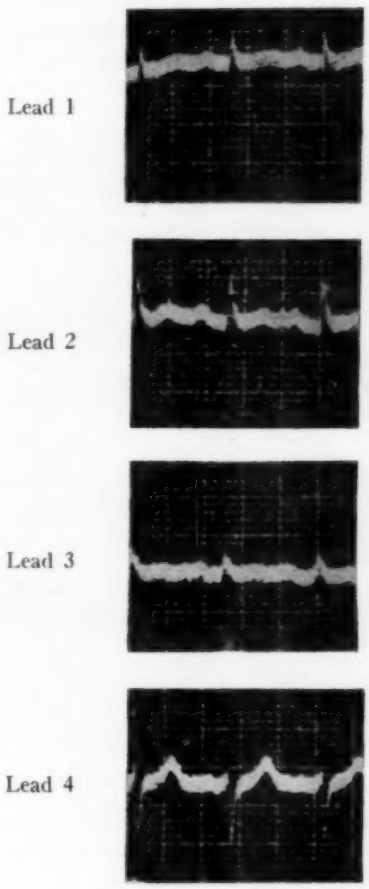


FIG. 2. Electrocardiogram taken August 13, 1945. The rate is 120. The QRS complexes are of low amplitude and slurred, the T waves are of low voltage.

Urinalysis disclosed proteinuria (3 plus), specific gravity 1.015, no sugar, blood or bile. Many granular casts and white blood cells were present. The blood urea nitrogen was 75 mg. per 100 c.c. The hemogram was not unusual. White blood cells were 11,850, hemoglobin 84 per cent, neutrophiles 79 per cent, lymphocytes 17 per cent, monocytes 1 per cent and eosinophiles 3 per cent. Smears for malaria were negative. The spinal fluid was normal except for elevation of protein to 100 mg. per 100 c.c. Stool examination was essentially negative. Roentgenograms of the chest showed exaggeration of markings of right root suggesting an atypical pneumonia or congestion. The heart contour was normal.

Supportive and symptomatic therapy was promptly instituted. The azotemia and dehydration were combated by the restoration of adequate fluid balance with dextrose-saline infusions. Sedation, maximum bed rest and oxygen were employed to counteract pulmonary and cardiac complications.

The clinical course was brief. The temperature varied from 101° to 103° F. accompanied by persistent sinus tachycardia (120 to 130 per minute) and tachypnea (28 to 50 per minte) (figure 1). The hypotension and poor heart sounds persisted. The venous pressure never exceeded 120 mm. of water. The breath sounds became suppressed posteriorly. Generalized muscle twitching became quite evident and delirium more marked. The electrocardiogram corroborated the clinical impression of severe myocarditis (figure 2).

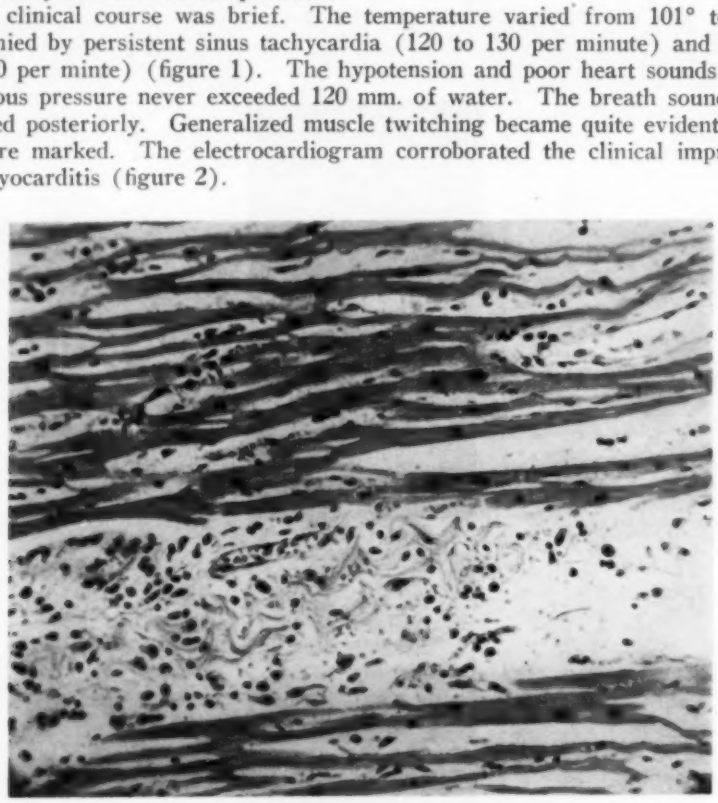


FIG. 3. Section of myocardium showing edema and diffuse interstitial cellular infiltration. Giemsa × 178.

Serum was examined August 14, 1945 for antibodies in the Weil-Felix test by the Division of Virus and Rickettsial Diseases of the Army Medical Center of the Army Medical School and the following results were obtained:

Proteus OX–19 negative
Proteus OX–2 negative
Proteus OX–K complete 1/160, partial 1/640

Serum obtained eight hours later was examined by the Second Service Command with results as follows:

Proteus OX–19 negative
Proteus OX–2 negative
Proteus OX–K positive 1/1,280

Fatal pulmonary edema occurred August 16, 1945 and autopsy was performed the same morning. The right lung weighed 1,060 grams and exhibited consolidation of the lateral half of the lower lobe. Microscopically, the pleura showed no attached

exudate. The cortical (sub-pleural) zone presented areas of vesicular emphysema. More deeply the acini were filled with albuminous material including a great many swollen lightly pigmented macrophages. The bronchioles were compressed. The heart weighed 370 grams. The entire myocardium was soft and flabby. On the upper surface of the mitral valve were minute firm vegetations extending into the left auricle microscopically, the epicardium was thin and showed interstitial cellular infiltration. The small coronary branches included in the sections studied displayed normal walls. The muscle fibers of the myocardium were broad and the striae well differentiated. Throughout the muscle wall of the heart there was edema and diffuse interstitial cellular infiltration consisting of plasma cells, small lymphocytes, scattered larger cells with acidophilic cytoplasm, possibly cells of the Anitschkow myocyte type (figure 3). The

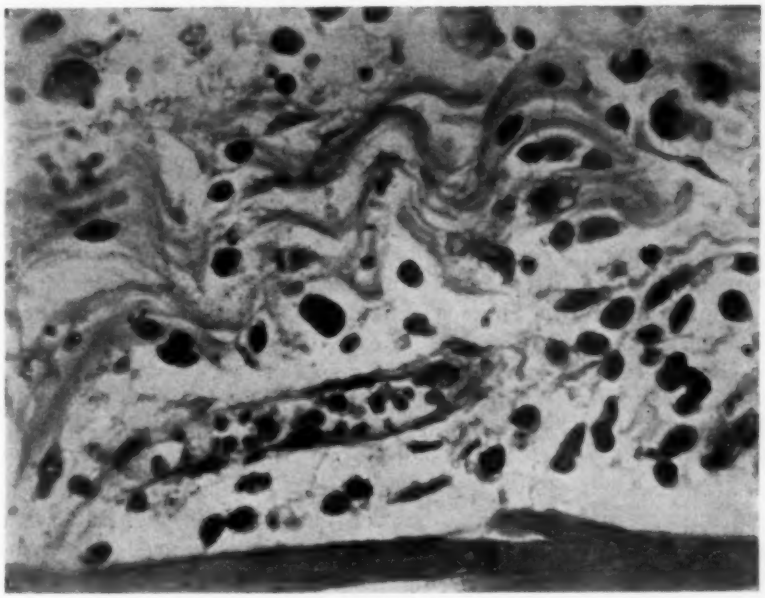


FIG. 4. Interstitial cellular infiltrate of myocardium showing numerous massed cells presenting plump granules. Giemsa × 563.

anterior cusp of the mitral valve revealed a thin base and thickened terminal segment of the valve. There was no increase in vascularity or cellular reaction. The "verrucosity" noted was regarded as "marantic," terminal, and not organic. The mural endocardium was thin and showed edema. Sections of the heart stained by Giemsa were particularly interesting. The interstitial cellular infiltrate included fairly numerous massed cells presenting plump granules, staining a plum color. A few cells regarded as pericytes (adventitial cells) included fairly dense clumps of very delicate cocco-bacillary forms staining a light blue. The cocco-bacillary forms resembled rickettsia (figure 4). Cells presenting rickettsia-like bodies are extremely rarely encountered in the type of sections studied. The spleen weighed 460 grams, was enlarged and extremely soft. The architecture was completely obliterated, and only a semi-fluid material remained within the capsule. Microscopic examination of a relatively intact small accessory spleen showed the trabeculae widely separated. The red pulp displayed a loss of normal architecture; the sinusoids were filled with cells of the granulocytic series showing a shift to the left. The liver weighed 2,290 grams and

appeared extremely congested. Microscopically, the architecture was preserved. There was venous congestion and congestion of the sinusoids. The sinusoids included many white blood cells, granulocytes and cells of the lymphocytic series. The liver cells were compressed, finely granular and displayed varying degrees of fat infiltration. The triads showed congestion of the terminal branches of the portal vein; one portal vein included a thrombus consisting of closely clumped coccal forms without cellular reaction. The kidneys appeared congested. Microscopically, the renal architecture was preserved. The cells lining the tubuli contorti were swollen and finely granular; the lumen of these tubules contained a finely granular acellular detritus. The terminal brush formation of the cells lining the convoluted tubules was fairly well preserved. There was ischemia, postmortem degeneration and cloudy swelling. The brain, grossly, showed moderate injection of the pial vessels. Microscopically, the sub-arachnoid showed congestion. The sub-arachnoid and the sub-pial zone displayed diffuse cellular infiltration consisting of cells of the lymphocytic series, some plasma cells and a few granulocytes. The cerebral cortex showed slight edema. The findings were those of congestion and slight cellular infiltration.

Discussion

Scrub typhus or tsutsugamushi fever is an acute febrile disease caused by *Rickettsia tsutsugamushi* (*Rickettsia orientalis*) and closely resembles the other members of the group of rickettsial infections.

This case emphasizes the salient feature of the disease. Air evacuation of the subject of this report to the United States from a highly endemic focus returned him within the incubation period of seven to 21 days. The absence of a primary eschar is common in Burma and India as opposed to its characteristic presence in most Asiatic regions. The clinical picture in this case embraced the characteristic findings of severe scrub typhus. Headache, malaise, nausea and deafness were present early as was mental cloudiness of increasing severity. Cyanosis, tachypnea, tachycardia and hypotension attested to the complicating atypical pneumonia and myocarditis. The euphoria, delirium, muscular twitchings and coma were evidence of dreaded central nervous system involvement. Histopathologic examinations corroborated the pathologic lesions described by Lipman et al.

As far as can be determined, this is the first reported case of scrub typhus introduced into the United States from an overseas theater.

Modern communication is bringing the diagnostic problems of tropical diseases to this country; a careful history, suspicion and awareness of their possibility will meet the diagnostic challenge successfully.

BIBLIOGRAPHY

1. Lipman, Bernard L., Casey, Adrian V., Byron, Robin A., and Evans, Edwin C.: Scrub typhus, War Med., 1944, vi, 5.

EDITORIAL

ON THE ETIOLOGY OF CANCER—COCARCINOGENIC AGENTS

DURING the fifteen years that have elapsed since the isolation of the carcinogenic substance benzpyrene from coal tar (Cook, Hewett, Hieger[1]), a relatively large number of substances have been tested for their cancer-producing potentialities. Cook and Kennaway[2, 3] surveyed the most important work up until 1938 and listed 860 papers in the bibliography. Over 1,000 compounds have been listed in a recent revision of Hartwell's extensive survey[4] of compounds that have been tested for carcinogenicity. Two hundred and sixty-four, or approximately one-fourth of the substances tested, have been shown to induce cancer. In the early part of this work on carcinogenic agents, considerable stress was laid on chemical structure. The possibility of establishing any chemical or standard pattern for carcinogenicity has gradually faded as the list of chemicals that have been successfully used to induce cancer has grown longer. This list now includes not only the potent steroidal compounds; methylcholanthrene, benzpyrene and dibenzanthracene; but such heterogeneous substances as carbon tetrachloride, urethane (to induce lung tumors), butter yellow or dimethylamino azobenzene (hepatomas), estrogens (breast cancer and uterine cancer), amino fluorene, beta naphthalamine, scarlet red dye, etc. Finally, but not less astonishing, 25 per cent glucose solutions have been used to induce cancer in rats.[5]

When we add to this list of over 250 chemicals the four regions of the electromagnetic spectrum that have been found to be carcinogenic (gamma rays, roentgen-rays, ultraviolet light, and heat), it makes an impressive list of agents for use in experimental cancer induction. As this list grows, the search for the cause or causes of cancer becomes not simpler, but more and more complex. There are many who think that the cause of neoplastic diseases will finally prove to be not a single factor, but that the causes will be as diverse as the neoplasms and the tissues affected.

The ease with which it is possible to induce cancer experimentally in mice and rats has led to the assumption that these agents would be equally carcinogenic in all other species. It is important to realize that they are not. As a matter of fact they have not been adequately tested even in such com-

[1] COOK, J. W., HEWETT, C. L., and HIEGER, I.: The isolation of a cancer-producing hydrocarbon from coal tar. Parts I, II and III, Jr. Chemical Soc., 1933, p. 395.

[2] COOK, J. W., and KENNAWAY, E. L.: Chemical compounds as carcinogenic agents. First supplementary report: Literature of 1937, Am. Jr. Cancer, (Bibliography), 1938, xxxiii, 50.

[3] COOK, J. W., and KENNAWAY, E. L.: Chemical compounds as carcinogenic agents. Second supplementary report: Literature of 1938 and 1939, Am. Jr. Cancer, 1940, xxxix, 381, 521.

[4] HARTWELL, J. L.: Survey of compounds which have been tested for carcinogenic activity, Nat. Inst. Health, Nat. Cancer Inst., U. S. Pub. Health Service, Bethesda, Md., 1941.

[5] NONAKA, T.: The occurrence of subcutaneous sarcomas in the rat after repeated injections of glucose solution, Gann, 1938, xxxii, 234.

mon laboratory animals as dogs, cats and guinea pigs. A summary [6] of the data tabulated in Hartwell's survey of carcinogenic compounds reveals this in a striking way. According to this summary approximately 9,000 or 42 per cent of 21,000 mice treated with one of the three most potent carcinogens (1,2,5,6 dibenzanthracene; 3,4 benzpyrene; 20 methylcholanthrene) developed tumors. Four thousand and eight hundred rats were treated with the same substances and 33 per cent or 1,600 developed tumors. Five hundred and twenty-nine rabbits yielded only 47 tumors or about 9 per cent; only 9 of 110 guinea pigs or 8 per cent developed tumors. It is remarkable that only 13 dogs are included in this comprehensive survey of the literature and no tumors resulted. Cats and monkeys were not even mentioned, so it would appear that these agents had not been tried at all in these animals. This is probably a false impression for cats and monkeys have doubtless been treated with these carcinogenic agents but the results of this work have failed to appear because of the general and unfortunate tendency to omit the publication of negative results. More recently there have appeared some brief notes on the drastic but unsuccessful attempts to induce cancer in monkeys with large doses of estrogens,[7, 8] methylcholanthrene,[8] and other agents.

It is evident that mice and rats exhibit a relatively great but variable sensitivity to the cancer-producing chemicals while other animals are more resistant. An attempt to discover the cause of this sensitivity led to the concept that the unique porphyrin metabolism which these rodents exhibit might be related to their high sensitivity.[6] The search for porphyrins in the organs and tissues of human subjects that show a high cancer incidence revealed that some of these organs and tissues (cervix of the uterus, skin of the face) are frequently subjected to excessive and abnormal concentrations of porphyrins.[6, 9, 10, 11] Porphyrins have also been used to increase the sensitivity of certain mice of so-called resistant strains. The porphyrins, when administered alone, have no carcinogenic action. When administered concurrently, however, they decrease the latent period for methylcholanthrene-induced tumors and ultraviolet light-induced tumors.[6] They also appear to increase the sensitivity of tissues to the action of estrogenic compounds.[6] Some of the porphyrins (protoporphyrin, mesoporphyrin, deuteroporphyrin) have therefore been classified as naturally occurring *cocarcinogenic* compounds.

[6] FIGGE, F. H. J.: The relationship of pyrrol compounds to carcinogenesis, A.A.A.S. Research Conference on Cancer, edited by F. R. Moulton, Science Press Printing Co., Lancaster, Pa., 1945, 117–128.

[7] ENGLE, E. T., KRAKOWER, C., and HAAGENSEN, C. D.: Estrogen administration to aged female monkeys with no resultant tumors, Cancer Res., 1943, iii, 858–866.

[8] ALLEN, E.: Report of activities during 1940 (p. 8), Report of activities during 1941 (p. 24), International Cancer Research Foundation.

[9] FIGGE, F. H. J.: Fluorescence studies on cancer. I. Porphyrin metabolism, Harderian gland fluorescence, and susceptibility to carcinogenic agents, Cancer Res., 1944, iv, 465–470.

[10] JONES, E. G., FIGGE, F. H. J., and HUNDLEY, J. M.: Fluorescence studies on cancer. II. The red fluorescence of the genitalia of women, Cancer Res., 1944, iv, 472–482.

[11] FIGGE, F. H. J., JONES, E. G., and WOLFE, G. F.: Fluorescence studies on cancer. III. The extraction and identification of porphyrins from the red-fluorescent exudates on the genitalia of women, Cancer Res., 1944, iv, 483–486.

The principle of cocarcinogenic action is not a new one. The term was first introduced by Shear [12, 13] to describe a non-carcinogenic fraction of coal tar that appeared to augment the activity of benzpyrene. This served to explain why the original tar was much more active than the purified benzpyrene which was extracted from it. The cocarcinogenic fraction in tar was not isolated or characterized and it is of interest in this connection that many coals and shale oils contain porphyrins. The term cocarcinogenic was next adopted by Berenblum [14] to describe the action of croton oils and resins. He found that croton oil alone was not carcinogenic but when this oil or resin extract was administered along with a very low, almost sub-carcinogenic, concentration of benzpyrene in acetone this resulted in a greatly increased carcinogenic potency. The cocarcinogenic action was not related to the irritant properties of croton oil. Other vesicants and irritants such as mustard gas and turpentine were not found to be cocarcinogenic when tested under identical conditions. Berenblum therefore defined cocarcinogenic action as the augmentation of carcinogenesis by a non-carcinogenic agent.

More recently, Bielschowsky [15] has described another type of cocarcinogenic action. He observed over 100 neoplasms in 93 Wistar rats which had been fed 4 milligrams of 2-acetylaminofluorene. The most of these tumors involved the liver, mammary gland and the external acoustic meatus. When he gave 2-acetylaminofluorene in combination with allyl-thiourea he observed a high incidence of adenocarcinoma of the thyroid glands.[16] Thus a compound of thiourea which normally produces only a hyperplasia of the thyroid gland when administered along with aminofluorene gave rise to neoplasms of the thyroid gland. In other words, a relatively weak non-specific carcinogen was converted to a potent one with more specific action. In this case, the specificity or site of action appeared to be controlled by the cocarcinogen.

The practical significance of these demonstrations of cocarcinogenic agents is that we must begin to consider not only the action of a single substance but also the influence it will have when administered along with other substances or with substances such as porphyrins which may be present naturally. In the examples cited, the carcinogenic combinations of substances have always included one substance which, by itself, acted as a weak carcinogenic agent and another substance, the cocarcinogen, which augmented the action of the so-called carcinogen. So far there have been no reports on cancer production by a combination of two substances which when administered singly never produce cancer.

[12] SHEAR, M. J.: Studies in carcinogenesis: methyl derivatives of 1:2-benzanthracene, Am. Jr. Cancer, 1938, xxxiii, 499–537.

[13] SALL, R. D., and SHEAR, M. J.: Studies on carcinogenesis. XII. Effect of the basic fraction of creosote oil in the production of tumors in mice by chemical carcinogens, Jr. Nat. Cancer Inst., 1940, i, 45–55.

[14] BERENBLUM, I.: The cocarcinogenic action of croton resin, Cancer Res., 1941, i, 44–48.

[15] BIELSCHOWSKY, F.: Distant tumors produced by 2-amino and 2-acetyl-amino-fluorene, Brit. Jr. Exper. Path., 1944, xxv, 1–4.

[16] BIELSCHOWSKY, F.: Tumors of the thyroid produced by 2-acetyl-amino-fluorene and allyl-thiourea, Brit. Jr. Exper. Path., 1944, xxv, 90–94.

Quite recently, however, a new hypothesis [17] has been introduced which may eventually cause us to modify our definition of a carcinogenic agent. According to this hypothesis the action of carcinogenic compounds depends on their ability to convert energy derived from cosmic and similar penetrating radiations into energy which induces cancer. In support of this hypothesis, lead plates ¼″ to ½″ thick, which intensify the effect of cosmic radiation, accelerate the rate of tumor induction by methylcholanthrene. Lead plates have also been used to increase the incidence of spontaneous mammary carcinomas in mice; and shielding from cosmic radiation showers decreased the spontaneous cancer incidence in mice of the same strain.[18]

If the hypothesis that cosmic radiation is a primary factor in carcinogenesis is true, then these diverse substances would not be carcinogenic in the absence of cosmic radiation and they would have to be regarded not as carcinogens but rather as cocarcinogens. It is doubtful, however, that cosmic radiation could produce cancer in the absence of these chemical agents, otherwise cancer would be more widespread and abundant than it is. We would thus have a situation in which a low intensity non-carcinogenic form of energy is converted into a carcinogenic form of energy by cocarcinogens which we now erroneously call carcinogenic agents. The possible augmentation of the action of this energy by substances such as porphyrins and croton oil would require the inclusion of additional cocarcinogens. According to this concept of cocarcinogenic action, cancer would be caused not by a single substance but by two, three or more non-carcinogenic interdependent agents.

F. H. J. FIGGE

[17] FIGGE, F. H. J.: Cosmic radiation and cancer, Science, 1947, cv, 323–325.
[18] EUGSTER, I., and HESS, V. F.: Weltraumstrahlung und ihre biologische Wirkung, 1940, Orell Füssli Verlag, Zurich-Leipzig.

REVIEWS

The Treatment of Peptic Ulcer. By GEORGE J. HEUER, M.D., assisted by CRANSTON HOLMAN, M.D., and WILLIAM A. COOPER, M.D. 118 pages; 16 × 23.5 cm. J. B. Lippincott Co., Philadelphia. 1944. Price, $3.00.

In this period in which the introduction of vagotomy as a surgical procedure in the treatment of peptic ulcer is under such active discussion, careful analyses of the results of surgical treatment by other methods are of timely interest. Particularly valuable is the reminder that the value of any one method can only be assessed after study of a considerable group of cases followed for from five to ten years.

Dr. Heuer's study, published in 1944, is based upon the follow-up of 1204 patients admitted to the New York Hospital and its Outpatient Department between 1932 and 1942 of whom 39.2 per cent were treated surgically within the period named. Of 732 patients whose initial treatment was medical the results were considered satisfactory in only 54.9 per cent. On the other hand the mortality due to ulcer in this group was 3.5 per cent.

It is interesting to note that the operative mortality plus the late mortality (due to ulcer causes) of cases treated by gastro-enterostomy was 5.9 per cent; but that the satisfactory results were assessed as 73.6 per cent of 201 cases.

A similar comparison of the medically treated cases with those treated by gastric resection shows that in the latter the total mortality (operative and later from ulcer causes) was 7.7 per cent and the percentage of satisfactory results was 83 per cent in 142 cases.

These figures then suggest that in peptic ulcer a higher percentage of satisfactory results is obtained by standard surgical procedures (exclusive of vagotomy) but at the expense of a distinct increase in the total mortality rate among those so treated above that observed in the medically treated cases. The significance of these findings, however, must be qualified by the fact that the surgically treated cases were a selected group which included a much higher percentage of severe or complicated cases than those treated exclusively by medical measures.

It would have been interesting if the author had drawn a comparison between the total mortality in the group who remained on medical treatment after having been advised to submit to operation and the group who because of a similarly unsatisfactory result from medical treatment were operated upon.

The reader will find far more in this little book than such general statistics on results as are referred to above. There are interesting discussions on the rôle of surgery in hemorrhage; on the value of gastro-enterostomy which the author feels still has a distinct place; on the results of operations for perforation; on the question of malignant changes in gastric ulcer.

It is not often that one encounters in any special field a more helpful monograph.

M. C. P.

Endocrine Function of the Hypophysis. By HARRY B. FRIEDGOOD, M.D.; Edited by HENRY A. CHRISTIAN, M.D., F.A.C.P. 828 pages; 16 × 24 cm. Oxford University Press, New York. 1946. Price, $4.50.

Although this is described in the preface as a monograph written for the physician, surgeon and investigator, its chief value would be to the investigator for whom it presents a comprehensive discussion of known and supposed hypophyseal functions with an unusually extensive bibliography. The physician or surgeon will find ade-

quate descriptions of acromegaly, giantism and dwarfism, but the spirit of the book is more investigative than clinical.

The first part of the book presents a detailed description of the anatomy, embryology and phylogeny of the hypophysis. Part two considers the cytophysiology and biochemistry of the anterior lobe of the hypophysis. The following two sections consider the factors affecting growth and the clinical disorders of growth. Part five discusses the functions of the neurohypophysis. The bibliographies attest to the extensive literature which Dr. Friedgood has reviewed in preparing this monograph. The accessibility of the material would be increased by a more detailed index.

J. Z. B.

Government in Public Health. By HARRY S. MUSTARD, B.S., M.D., LL.D. 219 pages; 21.5 × 14.5 cm. The Commonwealth Fund, New York, N. Y. 1945. Price, $1.50.

Though it was published in 1945, this small volume deserves review at this date in order to bring it again to the attention of physicians. The rapid extension of the field of public health is the most important trend in modern medicine. The historical development of this movement in the United States and its present status should be known to every physician and should be part of the education of every medical student. The character of future developments in this field is dependent upon an informed medical profession.

Dr. Mustard's book admirably fulfills its purpose of a critical but dispassionate survey of the development at local, state and federal levels of our present program of tax supported public health and medical care. He points out the importance of the practicing physician in public health. He discusses the relationship of voluntary medical programs and institutions to those under governmental control.

Though dealing with a subject which is controversial, the author keeps his book above the level of propaganda. One feels how much condensation and selection from a wealth of personal experience and historical research have been necessary to make possible the presentation in this small volume of such a factual, interesting and stimulating account of a complex problem.

M. C. P.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Acute Infectious Fevers (The). By ALEXANDER JOE, D.S.C., M.D., F.R.C.P., D.P.H., Medical Superintendent, City Hospital, Edinburgh; Lecturer on Infectious Diseases, University of Edinburgh, etc. 276 pages; 22.5 × 13.5 cm. 1947. The Blakiston Company, Philadelphia. Price, $4.50.

Color Atlas of Hematology, with Brief Clinical Descriptions of Various Diseases. By ROY R. KRACKE, M.D., Dean and Professor of Clinical Medicine, Medical College of Alabama. 204 pages; 24 × 16 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $5.00.

Diseases of the Chest, with Emphasis on X-Ray Diagnosis. By ELI H. RUBIN, M.D., F.A.C.P., F.C.C.P., Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital and Country Sanatorium, New York, etc. *Principles of Surgical Treatment (The).* By MORRIS RUBIN, B.A., M.D., Assistant Visiting Surgeon, Triboro Hospital and Morrisania City Hospital, New York, etc. 685 pages; 26.5 × 18.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $12.00.

Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner. (2nd Edition.) Edited by GARFIELD G. DUNCAN, M.D., Director of Medical Division, Pennsylvania Hospital, etc., with contributions by various others. 1045 pages; 25 × 17 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $12.00.

Gastritis. By RUDOLF SCHINDLER, M.D., F.A.C.P., Clinical Professor of Internal Medicine (Gastroenterology), College of Medical Evangelists, Los Angeles, etc. 462 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, $10.00.

Genetics, Medicine and Man. By H. J. MULLER of Indiana University; C. C. LITTLE of the Roscoe B. Jackson Memorial Laboratory; LAURENCE H. SNYDER of The Ohio State University. 158 pages; 23.5 × 15.5 cm. 1947. Cornell University Press, Ithaca, New York. Price, $2.25.

Human Gastric Function. An Experimental Study of a Man and His Stomach. (2nd Edition.) By STEWART WOLF, M.D., Assistant Professor of Medicine, Cornell University Medical College, and HAROLD G. WOLFF, M.D., Associate Professor of Medicine, Cornell University Medical College. 262 pages; 24.5 × 16 cm. 1947. Oxford University Press, New York. Price, $5.00.

Medical Aspects of Growing Old. By A. T. TODD, M.B. (Edin.), M.R.C.P. (Lond.), Honorary Physician, Bristol Royal Infirmary. 164 pages; 22.5 × 14.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, $3.50.

Methods of Vitamin Assay. Prepared and edited by The Association of Vitamin Chemists, Inc. 189 pages; 23.5 × 15.5 cm. 1947. Interscience Publishers, Inc., New York. Price, $3.50.

Penicillin Therapy. Including Streptomycin, Tyrothricin and Other Antibiotic Therapy (2nd Edition). By JOHN A. KOLMER, M.S., M.D., Dr. P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple University. 339 pages; 25.5 × 17.5 cm. 1947. D. Appleton-Century Company, New York-London. Price, $6.00.

Peripheral Vascular Diseases (Angiology) (2nd Edition). By SAUL S. SAMUELS, A.M., M.D., Consulting Vascular Surgeon, Long Beach Hospital, etc. 85 pages; 22 × 14 cm. 1947. Oxford University Press, New York. Price, $2.50.

Principles and Practice of Medicine (The) (16th Edition). CHRISTIAN-OSLER. 1539 pages; 24.5 × 16 cm. 1947. D. Appleton-Century Company, Inc., New York. Price, $10.00.

Pulmonary Tuberculosis: A Handbook for Students and Practitioners. By R. Y. KEERS, M.D., M.R.C.P., (Edin.), F.R.F.P.S. (Glas.), Medical Director, Red Cross Sanatoria of Scotland, etc., and B. G. RIGDEN, M.R.C.S. (Eng.), L.R.C.P. (Lond.), First Assistant Medical Officer, Red Cross Sanatoria of Scotland, etc., with a Foreword by F. H. YOUNG, O.B.E., M.D. (Camb.), F.R.C.P. (Lond.), D.P.H., Physician, Brompton Hospital for Consumption and Diseases of the Chest, etc. 227 pages; 19 ×12.5 cm. 1946. The Williams and Wilkins Company, Baltimore. Price, $5.00.

Recopilacion de Leyes, Reglamentaciones, Decretos y Resoluciones. Ministerio del Interior, Republica Argentina. 928 pages; 26.5 × 18 cm. 1945. Ministerio del Interior—La Camara de Diputados, Buenos Aires, Argentina.

Rh: Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions. By EDITH L. POTTER, M.D., Ph.D., Assistant Professor of Pathology, Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-In Hospital. 344 pages; 21 × 14.5 cm. 1947. Year Book Publishers, Chicago. Price, $5.50.

Textbook of Medicine (*A*) (7th Edition). Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; with the assistance of WALSH MCDERMOTT, M.D., Associate Professor of Medicine, Cornell University Medical College; Associate Editor for Diseases of the Nervous System, HAROLD G. WOLFF, M.D., Associate Professor of Neurology, Cornell University Medical College. 1730 pages; 26 × 18.5 cm. 1947. W. B. Saunders Company, Philadelphia. Price, $10.00.

Textbook of Medicine (8th Edition). By Various Authors. Edited by SIR JOHN CONYBEARE, K.B.E., M.C., D.M. Oxon., F.R.C.P., Physician to Guy's Hospital, London. 1170 pages; 22.5 × 14.5 cm. 1946. The Williams and Wilkins Company, Baltimore. Price, $8.00.

Textbook of Pathology (*A*) (6th Edition). By E. T. BELL, M.D., Professor of Pathology, University of Minnesota. Contributors: B. J. CLAWSON, M.D., Professor of Pathology, University of Minnesota; J. S. MCCARTNEY, M.D., Associate Professor of Pathology, University of Minnesota. 910 pages; 24 × 15.5 cm. 1947. Lea & Febiger, Philadelphia. Price, $10.00.

Tuberculosis as It Comes and Goes (2nd Edition). By EDWARD W. HAYES, M.D., F.A.C.P., Associate Professor of Tuberculosis, College of Medical Evangelists, etc., with Chapters by LAURENCE de RYCKE, Ph.D. 220 pages; 23 × 15 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $3.75.

COLLEGE NEWS NOTES

Additional Life Members

The College takes pleasure in announcing that the following Fellows became Life Members of the College as of the dates given:

Dr. Ralph H. Homan, El Paso, Tex., May 22, 1947
Dr. Nathan Worth Brown, Toledo, Ohio, May 23, 1947
Dr. George Miller Jones, Dallas, Tex., May 24, 1947
Dr. Paul Gross, Glenshaw, Pa., May 24, 1947
Dr. Verne S. Caviness, Raleigh, N. C., May 28, 1947
Dr. Harold J. Starr, Chattanooga, Tenn., May 29, 1947
Dr. Christopher J. McLoughlin, Atlanta, Ga., June 2, 1947
Dr. Clyde L. Mattas, Scranton, Pa., June 3, 1947
Dr. Roger S. Whitney, Colorado Springs, Colo., June 4, 1947
Dr. Louis A. Scarpellino, Kansas City, Mo., June 12, 1947

American College of Physicians Will Offer Postgraduate Courses during Autumn, 1947

More than 1,200 physicians registered in the postgraduate courses offered by the American College of Physicians during the past year. The popularity of these courses is growing and the practicability is being rapidly recognized.

While it is the preference of the Advisory Committee on Postgraduate Courses that the groups be limited to small numbers, it is necessary at the present time, in many instances, to admit larger groups because of the limited number of these short, intensive courses that are available.

Beginning with the autumn, 1947 courses, the tuition fees will be as follows:

(a) For small, limited, clinical courses:

Members of the College (per week), $60.00
Non-Members (per week), $120.00

(b) Regular courses:

Members of the College (per week), $30.00
Non-Members (per week), $60.00

The College will retain, to help defray administrative costs and other expenses, $5.00 of each candidate's fee and will remit the balance to the Director or institution where the course is given.

Proposed Schedule of Courses, Autumn, 1947

No.

1 Internal Medicine—University of Pittsburgh School of Medicine, Pittsburgh; Dr. R. R. Snowden, Director—two weeks, Sept. 1–13; Fee—A.C.P. Members, $60.00; Non-Members, $120.00

2 Psychosomatic Medicine—University of Colorado School of Medicine, Denver; Dr. Franklin G. Ebaugh, Director—two weeks, Sept. 8–20; Fee—A.C.P. Members, $60.00; Non-Members, $120.00

3 Hematology—Blood Disorders—Thorndike Memorial Laboratory, Boston City Hospital; Dr. William B. Castle, Director—one week, Oct. 13–18; Fee—A.C.P. Members, $30.00; Non-Members, $60.00

4 Physiological Basis for Internal Medicine—University of Pennsylvania School of Medicine, Philadelphia; Dr. Julius H. Comroe, Jr., Director—one week, Oct. 20–25; Fee—A.C.P. Members, $30.00; Non-Members, $60.00

5 Internal Medicine—University of Wisconsin Medical School, Madison; Dr. William S. Middleton, Director—two weeks, Nov. 3–14; Fee—A.C.P. Members, $60.00; Non-Members, $120.00

6 Advances in the Diagnosis and Treatment of Cardiovascular Disease—Massachusetts General Hospital, Boston; Dr. Paul D. White, Director—two weeks, Nov. 10–22; Fee—A.C.P. Members, $60.00; Non-Members, $120.00

7 Gastro-Enterology—Graduate Hospital of the University of Pennsylvania, Philadelphia; Dr. Henry L. Bockus, Director—1½ weeks, Nov. 17–26; Fee—A.C.P. Members, $45.00; Non-Members, $90.00

8 Internal Medicine—University of Texas School of Medicine, Galveston; Dr. Charles T. Stone, Director—two weeks, Dec. 1–13; Fee—A.C.P. Members, $60.00; Non-Members, $120.00

9 Mechanics of Disease—Peter Bent Brigham Hospital, Boston; Dr. George W. Thorn, Director—two weeks, dates and fees not yet determined.

10 Chemotherapy—New Drugs—Evans Memorial Hospital, Boston; Dr. Chester S. Keefer, Director—one week, dates and fees not yet determined.

At the time of release of this news item (June 18, 1947), the Committee is also considering a course in cardiology at Yale University School of Medicine, New Haven, under the directorship of Dr. H. M. Marvin, and a course in electrocardiography at Emory University School of Medicine, Atlanta, under the direction of Dr. R. Bruce Logue.

A preliminary Postgraduate Bulletin will be published by mid-summer and distributed to all members; however, members of the College desiring to make reservations in any of these courses may do so in advance by communicating directly with

Mr. E. R. Loveland, Executive Secretary
4200 Pine St.
Philadelphia 4, Pa.

Examinations by the American Board of Internal Medicine

A special oral examination will be held in Chicago October 8, 9 and 10, 1947. The date for closing acceptance of applications will be August 1, 1947.

The next written examination by this Board will be held in various centers over the country on October 20, 1947.

The oral examination is open only to those who have already passed the written portion of the examination. For filing applications or obtaining information, address

Dr. William A. Werrell
Assistant Secretary-Treasurer
American Board of Internal Medicine
1 W. Main St.
Madison 3, Wis.

Mid-West Regional Meeting and Postgraduate Course in Internal Medicine

The midwestern states, embracing Illinois, Indiana, Michigan, Minnesota, and Wisconsin, with invited participation by North Dakota, South Dakota, Nebraska, Wyoming, Montana, Iowa, and Kentucky, have determined upon holding their Regional Meeting at the Schroeder Hotel in Milwaukee, on Saturday, November 15,

following a two weeks postgraduate course in Internal Medicine at the University of Wisconsin Medical School, from November 3 to 14.

The postgraduate course will be under the official auspices of the College Committee on Postgraduate Courses, and will be directed by Dr. William S. Middleton. The registration will be limited to 25 members of the College. The course will be concluded by an all day Regional Meeting in Milwaukee. Dr. Karver L. Puestow, A.C.P. Governor for Wisconsin, is the Chairman of the Governors' Committee for the Regional Meeting; Dr. Francis D. Murphy, Milwaukee, is the local general chairman; Dr. Maurice Hardgrove, Milwaukee, is chairman of the Committee on Arrangements and Registration; Dr. Llewellyn R. Cole, who is coördinator of Graduate Medical Education at the Wisconsin Medical School, will be the Treasurer. A great deal of thought and enthusiasm are at work to produce an exceptional meeting. Further details and the program will be published in the near future.

Regional Meetings, 1947–48

Regional Meetings to occur during the fall or early winter of 1947 are in process of arrangement. A meeting for members of the College in Western Pennsylvania under the Chairmanship of the Governor for that area, will be held in Pittsburgh on September 10. This meeting will be a part of the postgraduate course in Internal Medicine, which is being given under the direction of the Governor, Dr. Roy R. Snowden, F.A.C.P., at that time. A meeting will be held at Oklahoma City on September 20 under the Chairmanship of Dr. Wann Langston, Governor for Oklahoma, for members of the College in Oklahoma. Members of the College residing in Western Michigan will hold a meeting at Muskegon at a date in October not yet selected. This meeting will be under the Chairmanship of Dr. William M. LeFevre, F.A.C.P. A Regional Meeting for North Carolina is being arranged to take place at Chapel Hill at some date during October or November. Dr. Robert L. McMillan, F.A.C.P., of Winston-Salem, will act as Chairman of the Program Committee. A meeting is planned to take place at Tampa, Fla., on December 8 and 9. Under the Governorship of Dr. Turner Z. Cason, F.A.C.P., and the Chairmanship of Dr. William C. Blake, F.A.C.P., Tampa, this meeting is planned for members of the College in Georgia, Alabama, and South Carolina.

The programs of these meetings and additional details will be published in subsequent issues of the Annals.

Mississippi Members Hold Regional Meeting at Biloxi

The annual luncheon meeting of the Mississippi members of the American College of Physicians was held May 7, 1947, during the Mississippi State Medical Society meetings at Biloxi, Miss. The attendance was good. The guest speaker was Dr. Thomas P. Findley, F.A.C.P., Assistant Professor of Medicine, Tulane University of Louisiana School of Medicine and member of the staff of the Ochsner Clinic, New Orleans, La. Dr. Findley's subject was "Clinical Aspects of Neurohypophyseal Functions."

American Board of Internal Medicine

The American Board of Internal Medicine has modified its regulations governing the number of written examinations authorized and the interval between written examinations.

Effective January 1, 1946, not more than three written examinations will be authorized. The interval between the first and the second written examinations will be one year. The interval between the second and third written examinations will be two years. A fee of five dollars ($5.00) is required for each additional written examination.

This ruling does not make it mandatory for a candidate to repeat the examination within one or two years, since each candidate may elect a larger interval. All written examinations are held on the third Monday in February and the third Monday in October of each year.

Not more than three oral examinations are authorized. The interval between the first and second oral examination will be one year. The interval between the second and third oral examination will be two years. A fee of ten dollars ($10.00) is required for each additional oral examination. Candidates may elect a larger interval if desired. The oral examinations are held regularly each year just in advance of the meetings of the American College of Physicians and the American Medical Association and at such other times and places as the Board may designate.

All candidates must pass the written examinations before admission to the oral is authorized. Oral examination in the sub-specialties recognized by this Board will be given at the time and place of the oral examination in general medicine. All candidates in a sub-specialty must file an application on a form provided for that purpose. All applications must be approved by the Advisory Board concerned and all candidates must have passed the oral examination in internal medicine before admission to the oral in a sub-specialty.

Advisory Committee on Postgraduate Courses

When the membership of the Advisory Committee on Postgraduate Courses was published in the May, 1947, issue, two appointments to that Committee had not yet been made. Dr. Walter L. Palmer, Chairman of the Board of Governors, has since appointed, as additional members of this committee, Dr. J. Edwin Wood, Jr., F.A.C.P., Charlottesville, Va., and Dr. Karver L. Puestow, F.A.C.P., both of whom are members of the Board of Governors:

Edward L. Bortz, *Chairman*, Philadelphia, Pa.
Edgar V. Allen, Rochester, Minn.
Turner Z. Cason, Jacksonville, Fla.
Karver L. Puestow, Madison, Wis.
J. Edwin Wood, Jr., Charlottesville, Va.

American Medical Association Meetings, Atlantic City, June 9–13

At the very interesting and well-attended Annual Meeting of the American Medical Association, which took place during the week of June 9–13, Dr. Edward L. Bortz, College Governor for Eastern Pennsylvania, was installed as President of the Association. Dr. Roscoe L. Sensenich, F.A.C.P., of South Bend, Ind., who has served as Chairman of the Board of Trustees of the Association, was elected to the position of President-elect. Dr. Sensenich will, therefore, succeed Dr. Bortz as President during the year 1948–49.

The Association decided during the meetings upon the following locations for Annual Meetings during the next three years: 1948, Chicago; 1949, Atlantic City; 1950, San Francisco.

Gifts to the College Library

Dr. John Mumford Swan, F.A.C.P., Rochester, New York has presented to the library of the American College of Physicians a copy of "Universa Medicina" by Iohannis Fernell II, as published in 1679. As was the custom of the day, the book is printed in Latin, possibly from wood cuts. The book contains approximately nine hundred pages, including a complete index, and is in a very excellent state of preservation.

Dr. James J. Waring, F.A.C.P., Denver, Colo., has presented a copy of the "Rocky Mountain Conference on Infantile Paralysis," published by the University of Colorado School of Medicine and Hospitals.

Redistribution of Territory to Governors for Eastern and Western New York

On recommendations of Dr. Edward C. Reifenstein, Sr., College Governor for Western New York, and Dr. Asa L. Lincoln, College Governor for Eastern New York, the Board of Regents has re-assigned New York territory as follows: henceforth, Western New York shall include not only all of Western New York, but also Northern New York, down to Albany, and all territory west of a line joining Albany with Binghamton. Eastern New York shall include all territory East or South of the connecting line between Albany and Binghamton. It is felt that this division is more in keeping with the interests of local groups as well as a more appropriate numerical distribution. Members in greater New York and closely adjoining territory probably have less interest and much less contact with members in the State at large.

Dr. Frederick A. Johansen, Medical Director (R), USPHS, F.A.C.P., has succeeded Dr. Guy H. Faget, USPHS, F.A.C.P., as Medical Officer in charge of the U. S. Marine Hospital, Carville, La.

The Legion of Merit has been bestowed on Dr. E. Rankin Denny, F.A.C.P., Tulsa, Okla. In the citation reference is made to the studies which Dr. Denny conducted at the Gardiner General Hospital, Chicago, on the action of penicillin. Dr. Denny served in the Army of the United States.

Members of the College are actively engaged in the work of the Wayne County, Mich., Medical Society. Officers for the year 1947–48 include, as President-elect, Dr. Douglas Donald, F.A.C.P., and College Governor for Michigan; as Trustee, Dr. Edward D. Spalding, F.A.C.P.; as Chairman of the Medical Section, Dr. Robert J. Schneck, F.A.C.P.; and as Secretary of the Medical Section, Dr. Sidney Adler, F.A.C.P. Drs. James J. Lightbody, F.A.C.P., and Ralph A. Johnson (Associate), are serving as Associate Editors of the Detroit Medical News.

On the occasion of the Annual Luncheon of the California Tuberculosis Association on March 29, 1947, medals were presented to Dr. Frank M. Pottenger, Sr., F.A.C.P., Monrovia, and Dr. George H. Evans, F.A.C.P., San Francisco. The medals recognized the extensive and distinguished contributions of Drs. Pottenger and Evans to our knowledge of the subject of tuberculosis.

Dr. James Morison Faulkner, F.A.C.P., Boston, became Dean of the Boston University School of Medicine on June 1. Dr. Faulkner is a graduate of the Harvard Medical School and a former resident of the Hospital of the Rockefeller Institute and the Johns Hopkins Hospital. Prior to his entry into the Medical Corps, U. S. Naval Reserve, during the recent War, Dr. Faulkner was a member of the faculty of the Boston University School of Medicine, and Physician and Cardiologist in the Massachusetts Memorial Hospitals. In 1946 Dr. Faulkner was appointed Professor of Medicine in the Tufts College Medical School and Director of the first and third Medical Services at the Boston City Hospital.

On June 1 Brigadier General Raymond W. Bliss succeeded Major General Norman T. Kirk, F.A.C.P., as Surgeon General of the United States Army, for a term of four years. Dr. Bliss, who entered the Army in 1911, graduated from the Tufts College Medical School in 1910. He subsequently attended the Army Medical School and received special training in Surgery at Harvard. From January, 1946, until this June he was Deputy Surgeon General.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to June 17, 1947 inclusive).

Arden Freer, Neversink, N. Y. (Col., MC, USA)
Samuel Edward King, New York, N. Y. (Lt. Col. MC, AUS)
H. Beckett Lang, Albany, N. Y. (Comdr., MC, USNR)
Richard M. McKean, Detroit, Mich. (Col., MC, AUS)
Jerome T. Paul, Chicago, Ill. (Major, MC, AUS)
Nathaniel E. Reich, Brooklyn, N. Y. (Major, MC, AUS)
Donald S. Smith, Pontiac, Mich. (Lt. Comdr., MC, USN)

RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948 to June 30, 1949. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

The stipend will be from $2,200 to $3,000.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

ABRIDGED MINUTES, BOARD OF REGENTS

FIRST MEETING

CHICAGO, ILL.

APRIL 27, 1947

The first meeting of the Board of Regents during the 28th Annual Session of the American College of Physicians convened at 2:00 p.m., April 27, 1947, at the Palmer House, Chicago, President David P. Barr presiding, with Mr. E. R. Loveland acting as Secretary and with the following in attendance:

David P. Barr	*President*
Hugh J. Morgan	*President-Elect*
James J. Waring	*1st Vice President*
A. B. Brower	*2nd Vice President*
T. Homer Coffen	*3rd Vice President*
William D. Stroud	*Treasurer*
George Morris Piersol	*Secretary General*
Maurice C. Pincoffs	*Editor*
Chauncey W. Dowden	*Chairman, Board of Governors*
Francis G. Blake	
James F. Churchill	
Reginald Fitz	
Roger I. Lee	
Charles T. Stone	
Walter B. Martin	
William S. Middleton	
James E. Paullin	
LeRoy H. Sloan	
George F. Strong	
Ernest E. Irons	
William S. McCann	
T. Grier Miller	
Charles F. Moffatt	
Charles F. Tenney	

Abstracted minutes of the previous meeting of the Board were read by the Secretary and by resolution approved as read.

President Barr invited Mr. Royal Ryan of the New York Convention Bureau to present an invitation from New York City for the College to meet there in 1948. After presenting an invitation on behalf of the civic bodies, the County Medical Society, and the New York Academy of Medicine, and describing New York's facilities, Mr. Ryan answered numerous questions and retired. It was explained that the meeting city for 1948 would be selected by the new Board of Regents at its meeting on Friday, May 2.

President Barr requested Dr. Hugh J. Morgan to present a Memorial to the late Dr. James D. Bruce in accordance with directions of the Board of Regents at its previous meeting, whereupon Dr. Morgan read the following Memorial which was approved, spread upon the minutes, and a copy authorized to be sent to Mrs. Bruce:

"IN MEMORIAM

JAMES DEACON BRUCE

1872–1946

"James Deacon Bruce, a Fellow of the American College of Physicians since 1925, died at Ann Arbor, Michigan, September 5, 1946. He served as Governor, Regent and President of the College. His many and notable contributions to medical education and medical statesmanship in this country have been reviewed and evaluated by Dr. H. H. Riecker in the ANNALS OF INTERNAL MEDICINE.

"As a member of this Board of Regents and a patron of the College, he was outstanding; but, we, of the Board, do not cherish his memory for this reason alone, nor was it for this reason alone when he was with us that we most appreciated him.

"He was cultured and not merely learned; he used his wit for merriment and not malice; he was candid without tactlessness, and friendly without affectation. In the Board of Regents, his companionship was a privilege and a joy to all. Whether in the rôle of presiding officer or participant in debate, his humor, charm and courtesy were as unfailing as his wisdom and idealism. His discussions of matters under consideration by the Board were marked by simplicity, dignity and forcefulness and they revealed the high ideals and purposes of his life.

"This small tribute, all the more because it is the expression of our sincere sorrow, must fall short of doing justice either to the sentiments of the members of the Board of Regents or to the worth of our friend. We mourn his passing; we are grateful for our association with him, and we shall remember him always with affection and pride."

At direction of the President, the Secretary, Mr. Loveland, presented the following communications:

(1) Notification from Dr. James J. Waring of his resignation from the American Board of Internal Medicine on June 30, 1947, with a memorandum of the fact that his unexpired term is two years, or until June 30, 1949.

(2) Notification from the American Board of Internal Medicine that the terms of Drs. Cecil J. Watson, William S. McCann, and William B. Porter, appointees of the American College of Physicians on the Board, will expire July 1, 1947, with a notation that all three are eligible for re-appointment.

(3) An announcement that Dr. Robert B. Radl, Bismarck, had been appointed, by the President, Interim Governor for North Dakota, to act until the next regular election, due to the death of Dr. Julius O. Arnson, Governor for that state. The By-Laws provide that the President shall make interim appointments until the next regular election.

(4) A report that President Barr had appointed Dr. William Gerry Morgan, M.A.C.P., representative of the College at the annual meeting of the Gorgas Memorial Institute of Tropical Medicine.

(5) An announcement that President Barr had appointed Dr. Harry Plummer Ross, F.A.C.P., to represent the College at the inauguration of Thomas Elsa Jones, seventh President of Earlham College.

(6) Announcement that President Barr had appointed Dr. Francisco de P. Miranda, F.A.C.P., College Governor for Mexico, as official representative of the College at the inaugural ceremonies of the Hospital de Enfermedades de la Nutricion.

(7) An announcement that President Barr had appointed Dr. Walter Freeman, F.A.C.P., representative of the College in the Division of Medical Sciences

of the National Research Council, for a three-year term from July 1, 1947, to succeed Dr. Wallace M. Yater whose term will have expired at that time.

(8) An announcement that President Barr had appointed Dr. George Morris Piersol, F.A.C.P., and Dr. Edward L. Bortz, F.A.C.P., as representatives of the College to a recent UNESCO meeting at Philadelphia, March 24–26, 1947.

(9) A communication from Science Service proposing to issue privilege cards to members of the American College of Physicians, entitling each to a special subscription rate to the "Science News Letter."

(Upon motion regularly made and seconded, it was voted not to take advantage of this offer by Science Service.)

(10) A recommendation from the Marshal, Dr. T. Grier Miller, that the names of newly elected Fellows be not formally read at the Convocation, but that their names be included in a published roster which shall be handed by the Chairman of the Committee on Credentials to the President during the induction ceremonies.

(It was moved by Dr. Paullin and seconded by Dr. Brower that the recommendation of the Marshal be approved. There followed a discussion in which Dr. Fitz pointed out that a survey had been made some years ago which resulted in an indication that the reading of the names of new Fellows is a procedure well worth carrying forward. This survey had been made among the younger and newer Fellows of the College who felt the reading of the names a minimal recognition. The motion was put to vote and adopted with 17 voting in favor and 6 against.)

(11) A letter of appreciation from Dr. David D. Rutstein, Medical Director of the American Council on Rheumatic Fever, acknowledging receipt of the gift of $1,000.00 by the American College of Physicians toward the work of that Council.

(12) A letter of acknowledgment and appreciation from the Secretary of the University of Chicago, Board of Trustees, for a donation of $1,730.87, proceeds from a postgraduate course directed by Dr. Walter L. Palmer for the American College of Physicians, the donation being in support of a Fellowship in gastro-enterology at that institution.

(13) A report from Dr. George C. Griffith, F.A.C.P., Director of one of the College courses in cardiology during the spring of the current year, in which Dr. Griffith reported a surplus of somewhat over $500.00, which had been turned over to the College Governor for Southern California, Dr. Leland Hawkins, for use by the College for postgraduate activities in that region.

(14) A letter from Dr. Edgar V. Allen, F.A.C.P., Director of a recent course in peripheral vascular disease at the Mayo Foundation, under the auspices of the College, requesting approval by the College to turn over a surplus of $453.46 from the course to the George Brown Memorial Lectureship Fund. Faculty members on the course are not permitted to receive fees for their services and Dr. Allen, therefore, recommended this manner of disposing of the balance, especially in view of the fact that the fund had been substantially depleted.

(It was moved by Dr. Lee and seconded by Dr. Fitz that the fund be expended as suggested in Dr. Allen's letter. There was a general discussion in which the thought was expressed that funds contributed for postgraduate courses offered by the

College ought not to be spent for any other than strictly College purposes. It was, however, pointed out that all tuition fees collected by the College heretofore are turned over to the Director of the course for use by him or his institution in whatever manner he may select. In some instances such funds have been used for Fellowships, for additions to the library fund of the school, and, in other instances, have been distributed pro rata to the faculty. Dr. Churchill advocated that the College establish a definite policy for the future. President Barr advised against specifying exactly how these funds shall be used, because custom might vary greatly in different places and it might be embarrassing to have to conform to a very specific rule. The motion was put to vote and carried.)

(15) A letter addressed to the Board of Regents from Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., concerning the American Board of Internal Medicine, with special reference to the abolition of preceptorships and the new type of "multiple choice" examinations initiated during October, 1946. Dr. Yater suggested that the American College of Physicians and the Section on Medicine of the American Medical Association have a greater part than at present in determining the policies of the Board.

President Barr questioned whether the letter was in such form as could be submitted to action by the Board of Regents at the time and he called upon Dr. Waring, Chairman of the American Board of Internal Medicine, for comments.

Dr. Waring expressed with great sincerity and conviction his explicit confidence in the American Board as it was constituted in the past and as it is now constituted. He commended the earnest, hard-working, thoughtful group of men who are members of the Board. He stated that the preceptorship plan had been a sad failure but gave assurances that the Board, after careful study, was prepared to offer a substitute for the preceptorship plan which will satisfy all critics of the Board. In regard to the new type of examination, he pointed out the utter impossibility of individually grading the essay type of examination for the ever growing number of candidates for certification. He said also that it is common knowledge that many of the departments of education in some of our best universities feel that the essay type of examination is a poor medium to explore the depths and the efficiency of a man's knowledge in any particular subject. Dr. Waring said further that the Board had been fortunate in having among its members at least three men who had had much experience with the new type of multiple choice examinations, and that from their experience, the Board will refine, improve and perfect the new type of examination suitable to this particular organization. He admitted that the mortality in the October, 1946, examination had been high, partly due to insufficient experience in submitting the new type of examination and partly due to the fact that the Board had set its standards a little high on that particular occasion.

Dr. Irons said the Board of Internal Medicine needs no defense. He discussed, at some length, the matter of preceptorships and the new multiple choice type of examination. He emphasized that on all occasions the Board of Internal Medicine has taken great care to avoid unfairness. He recommended that the American Board of Internal Medicine should not be dominated by the American College of Physicians or the Section on Internal Medicine of the American Medical Association, but should remain autonomous—loss of autonomy would introduce, in Dr. Irons' opinion, a number of elements of danger.

Dr. McCann, a member of the Board of Internal Medicine, explained at some length the basic principles and objectives and operation of the multiple choice type of examinations, adding, "I think that there is one valuable thing that comes from this method of examination and that is the questions themselves can be assessed. After our first effort, we heard grumbling because some questions appeared to have two or three correct answers, and, of course, they were keyed for just one. The questions

have been subjected to analysis in this way: If the candidates are divided into three groups, the high group, the middle group, and the low group, and the percentage of men getting the keyed answer in each group is compared, a good question is one which will have a high percentage of correct answers in the top group, a lesser percentage in the middle group and a small percentage in the lower group. A question that gives fairly uniform results throughout the three groups is not a good question; it is too easy. A question that has a low score in the high group is either wrong or too hard—probably it is a wrong question. These problems are being studied in that way and as examinations go on and experience accumulates, the examinations will be better."

(A motion to refer Dr. Yater's letter to the American Board of Internal Medicine had been made by Dr. Lee, seconded by Dr. Stroud, and following the above discussion, was adopted.)

Communications Continued:

(16) A letter from Dr. E. J. Kepler, submitted through Dr. Edgar V. Allen, inquiring about the possibilities of conferring an honorary Fellowship upon an eminent Buenos Aires internist. Dr. Kepler had been informed that the By-Laws of the College do not provide in any manner for honorary Fellowships.

(17) A letter from Dr. Nelson G. Russell, suggesting that the College should have a hood representing the organization for use of its representatives at academic functions. The Board was reminded that this matter was carefully studied several years ago with the result that the College adopted an official Fellowship Chevron to be worn on the academic gown on such occasions.

(18) An inquiry from Dr. Karl Rothschild, F.A.C.P., regarding eligibility of candidates holding honorary medical degrees. The Secretary pointed out that the By-Laws provide, "A candidate shall be a graduate of an approved medical school."

(After some discussion, it was moved by Dr. Piersol, seconded by Dr. Brower, and carried, that honorary medical degrees cannot be recognized in the College as the equivalent of a Degree of Medicine.)

New Business

The Secretary reported that in accordance with the By-Laws of the College, one Fellow had been dropped from the Roster as of the current day because of delinquency in dues of two years or more. It was pointed out that this is a most unusual record to have but one member dropped for delinquency out of the entire membership.

Report of the Secretary General, Dr. George Morris Piersol: "Deaths since the last meeting of this Board include 32 Fellows and 4 Associates as follows:

"Fellows

Arnson, Julius O.	Bismarck, N. D.	October 29, 1946
Barbash, Samuel	Atlantic City, N. J.	November 14, 1946
Beling, Christopher Charles	Newark, N. J.	November 30, 1946
Benoit, Emmanuel P.	Montreal, Que., Can.	April 14, 1946
Briskman, A. Lee	Denver, Colo.	November 26, 1946
Brown, Mark A.	Cincinnati, Ohio	January 13, 1947
Chapman, George A.	Glens Falls, N. Y.	December 16, 1946
Deaderick, William H.	Hot Springs National Park, Ark.	March 11, 1945

Eschweiler, Paul C.	Little Rock, Ark.	August 23, 1946
Favill, John	Chicago, Ill.	December 21, 1946
Fish, Clyde Mulhollon	Pleasantville, N. J.	November 21, 1946
Flynn, James Murray	Rochester, N. Y.	December 14, 1946
Gaumer, James Stewart	Fairfield, Iowa	September 9, 1946
Hardisty, Richard H. M.	Montreal, Que., Can.	November 12, 1946
Held, Isidore William	New York, N. Y.	March 2, 1947
Hill, Harold Phillips	San Francisco, Calif.	December 3, 1946
Johnson, Trimble	Atlanta, Ga.	October 6, 1946
McBride, Robert E.	Las Cruces, N. M.	January 17, 1947
McCain, Paul Pressly	Sanatorium, N. C.	November 25, 1946
Mount, Frank R.	Portland, Ore.	October 11, 1946
O'Mara, John T.	Baltimore, Md.	March 3, 1946
Preston, John William	Roanoke, Va.	January 1, 1947
Rosenfeld, Joseph	Youngstown, Ohio	November 4, 1946
Roses Artau, Miguel	San Juan, P. R.	July 17, 1945
Roth, Paul	Battle Creek, Mich.	November 6, 1946
Sargent, Ara N.	Salem, Mass.	August 26, 1946
Schleiter, Howard G.	Pittsburgh, Pa.	February 5, 1947
Shearer, Thomas Laidlaw	Baltimore, Md.	December 13, 1946
Todd, Lucius Newton	Augusta, Ga.	December 12, 1946
Topmoeller, George B.	Cincinnati, Ohio	October 3, 1946
Van Valzah, Robert	Goby, Va.	November 23, 1946
Wilson, Frank Wiley	M.C., U. S. Army	April 20, 1946

"*Associates*

Nelson, Parley	Rexburg, Idaho	September 12, 1946
Rosenblum, Alex Morton	Youngstown, Ohio	September 6, 1946
Stoneburner, Lewis T., III	Richmond, Va.	November 10, 1944
Waud, Sydney Peyster	Chicago, Ill.	October 19, 1946

"There may be other deaths that have not yet been reported.

"There are 119 new and additional life members, bringing the grand total to 612, of whom 46 are deceased, leaving a balance of 566. The names of the new life members are as follows (listed in order of subscription):

"Henry Monroe Moses	Brooklyn, N. Y.
Henry Weyler	Providence, R. I.
William E. G. Lancaster	Fargo, N. D.
Andrew Blair	Charlotte, N. C.
Paul F. Liva	Lyndhurst, N. J.
J. K. Williams Wood	Troy, Pa.
C. DeWitt Briscoe	Panama, R. P.
Carol C. Turner	Memphis, Tenn.
John Russell Twiss	New York, N. Y.
William R. Blue	Memphis, Tenn.
William M. Sheppe	Wheeling, W. Va.
Hildegarde G. Sinnock	Quincy, Ill.
George L. Steele	Springfield, Mass.
John I. Marker	Davenport, Iowa
Lorenzo D. Massey	Osceola, Ark.
Felix R. Park	Tulsa, Okla.
Samuel Goodman	Tulsa, Okla.
E. Cooper Cole	Toronto, Ont., Canada

Murray DeArmond	Indianapolis, Ind.
Joseph F. Hamilton	Memphis, Tenn.
W. LeRoy Dunn	Washington, D. C.
Harold K. Eynon	Collingswood, N. J.
Evert A. Bancker	Atlanta, Ga.
Hugh E. Kiene	Providence, R. I.
Isidore Lattman	Washington, D. C.
Lemuel C. McGee	Wilmington, Del.
Matthew Molitch	Atlantic City, N. J.
Glenn Edward Drewyer	Glenwood Springs, Colo.
Carl H. Fortune	Lexington, Ky.
Frank F. D. Reckord	Harrisburg, Pa.
Charles Windwer	Brooklyn, N. Y.
Samuel C. Arnett, Jr.	Lubbock, Tex.
Frank C. Clifford	Toledo, Ohio
Charles W. McClure	Boston, Mass.
Ernest G. McEwen	Evanston, Ill.
John B. D'Albora	Brooklyn, N. Y.
Richard F. Herndon	Springfield, Ill.
Mary McIndoe Spears	Philadelphia, Pa.
William Stein	New Brunswick, N. J.
Kenneth Taylor	New York, N. Y.
Clarence L. Andrews	Atlantic City, N. J.
John V. Barrow	Los Angeles, Calif.
Roland Cummings	Los Angeles, Calif.
Frederick K. Herpel	West Palm Beach, Fla.
Donald L. Kegaries	Rapid City, S. D.
Clyde H. Kelchner	Allentown, Pa.
Elmer A. Kleefield	Forest Hills, N. Y.
Robert C. Levy	Chicago, Ill.
Samuel A. Munford	Clifton Springs, N. Y.
Joseph Maxime Perret	New Orleans, La.
E. Clarence Rice	Washington, D. C.
Horace R. Livengood	Elizabeth, N. J.
Gordon Botkin Wilder	Anderson, Ind.
Cleo Russel Gatley	Pontiac, Mich.
Roy S. Leadingham	Atlanta, Ga.
George T. Strodl	New York, N. Y.
Leslie R. Webb	Springfield, Mo.
Otto G. Wiedman	Hartford, Conn.
Gordon R. Kamman	St. Paul, Minn.
Frank B. Queen	Portland, Ore.
F. Eugene Zemp	Columbia, S. C.
Edwin F. Hirsch	Chicago, Ill.
O. B. Kiel	Wichita Falls, Tex.
Albert H. Rowe	Oakland, Calif.
Madelaine R. Brown	Boston, Mass.
Hubert M. Parker	Kansas City, Mo.
Harry Ernest Flansburg	Lincoln, Nebr.
James E. Hunter	Seattle, Wash.
Wingate M. Johnson	Winston-Salem, N. C.
Flavius Downs Mohle	Houston, Tex.

Clarence W. Olsen	Beverly Hills, Calif.
Cecil L. Rudesill	Indianapolis, Ind.
Jacob Schwartz	Brooklyn, N. Y.
Joseph Kaufmann	Montreal, Que., Canada
James Thomas Gilbert, Jr.	Bowling Green, Ky.
Edward Urbane Reed	Los Angeles, Calif.
Paul J. Breslich	Minot, N. D.
B. Smith Hopkins, Jr.	Urbana, Ill.
Albert A. Hornor	Boston, Mass.
Kenneth Kyler Sherwood	Seattle, Wash.
Theodore F. Bach	Philadelphia, Pa.
Harold I. Kinsey	Toronto, Ont., Canada
Edward C. Reifenstein, Sr.	Syracuse, N. Y.
Rufus S. Reeves	Philadelphia, Pa.
H. Milton Rogers	St. Petersburg, Fla.
Joseph Weinstein	Brooklyn, N. Y.
James Clyde Waddell	Beatrice, Nebr.
Maurice Anthony Donovan	Schenectady, N. Y.
Thomas Balfour Dunn	Oakland, Calif.
Charles E. Leonard	Oklahoma City, Okla.
Pablo Morales-Otero	Santurce, P. R.
Robert P. Wallace	New York, N. Y.
William W. Fox	Atlantic City, N. J.
Carl O. Rinder	Chicago, Ill.
Amadeo Vicente-Mastellari	Panama, R. P.
Carl A. Hartung	Chattanooga, Tenn.
William C. Menninger	Topeka, Kans.
Robert S. Dow	Portland, Ore.
Arthur Lee Osterman	Wheeling, W. Va.
Everett E. Hammonds	Birmingham, Mich.
Henry Clay Long	Knoxville, Tenn.
Delbert H. McNamara	Santa Barbara, Calif
Aldis A. Johnson	Council Bluffs, Iowa
George O. Solem	Chicago, Ill.
Edward C. Koenig	Buffalo, N. Y.
James Steele	Brooklyn, N. Y.
James R. Gudger	New York, N. Y.
John Noll, Jr.	Youngstown, Ohio
Henry Allen Tadgell	Belchertown, Mass.
Harry L. Huber	Chicago, Ill.
George F. Lull	Chicago, Ill.
Robert Henry Southcombe	Spokane, Wash.
Richard Francis McLaughlin	Burlingame, Calif.
Dwight Locke Wilbur	San Francisco, Calif.
Henry Cook Macatee	Washington, D. C.
Abraham S. Rubnitz	Omaha, Nebr.
William Miller Dugan	Indianapolis, Ind.
Abraham Klein	Brooklyn, N. Y.
Saul Solomon	New York, N. Y."

It was pointed out that more life members have been added during the preceding twelve months than for any other like period in the history of the College.

(The report of the Secretary General was accepted by resolution.)

Report of the Committee to Study the Bruce Memorial Medal, Dr. George Morris Piersol reporting in the place of the Chairman, Dr. O. H. Perry Pepper: "Dr. Pepper and I, who constitute this Committee, held several meetings and arrived at the following recommendations: It is our well considered opinion that the present medal used by the College for the Phillips Memorial Award should also be used for the James D. Bruce Memorial Medal, appropriately changing the name and the inscription to meet the altered situations. It seems unnecessarily expensive and time consuming to have a new medal designed. As a general principle, we see no reason why the College cannot use the same medal for all awards, changing the inscription each time."

(On motion by Dr. Stroud, seconded by Dr. Morgan, and carried, the above report was approved.)

Report, Committee on Credentials, Dr. George Morris Piersol, Chairman: "The Committee on Credentials held a two-day meeting at the Philadelphia Headquarters on March 29–30, and a meeting at Chicago on the morning of April 27. At the March meeting there were a number of communications:

"(*a*) At the instance of Dr. C. F. Moffatt, Regent, Montreal, the Committee considered Fellowship in the Royal College of Physicians and Surgeons of Canada, of England and of Edinburgh. Already with the approval of the Board of Regents, the Committee recognizes certification by the Royal College of Physicians and Surgeons of Canada as acceptable in lieu of certification by the American Board of Internal Medicine. The Committee has reviewed the requirements for Fellowship in the Royal Colleges of England and Edinburgh, through Dr. Moffatt, and now wishes to recommend to the Board of Regents that Fellowship in any of the above Colleges may be accepted in lieu of certification by the Royal College of Physicians and Surgeons of Canada or the American Board of Internal Medicine."

DR. MOFFATT: When I communicated with Mr. Loveland, it was with the understanding then that the F.R.C.P., London and Edinburgh, were acceptable to the Royal College of Physicians and Surgeons of Canada. I now find that the Royal College of Physicians and Surgeons of Canada has raised its standards so that it will not now automatically accept F.R.C.P., London and Edinburgh. It feels that its standards are as high as any other body and it will not automatically accept these two other degrees.

PRESIDENT BARR: In the enlightenment of this statement by Dr. Moffatt, the Credentials Committee may wish to reconsider this matter before presenting it as a recommendation.

DR. PIERSOL: We withdraw this recommendation in lieu of the information that was not previously available.

Continuing the Report:

"(*b*) A communication was received concerning the status of the specialty of Physical Medicine. The Chairman pointed out that time will clarify this situation because a separate board of certification in Physical Medicine is now being organized.

"(*c*) The Committee reviewed the case of Dr. William D. Mackay (Associate) of Salisbury, Conn., who was elected on April 19, 1942, and a few months thereafter had to retire from practice due to illness. For the entire intervening period he has been ill and living on a farm, unable to make any medical progress whatsoever, or to become certified. Now, at the end of his Associate term, he has largely regained his health and expects in the next few months to return to the practice of medicine on a limited scale in New York City. The Committee appreciates that the strict interpretation of the regulations limiting Associateship to a maximum of five years

visited an unfair hardship upon this candidate, and that on occasion there might be one or more other candidates likewise unfortunate. The Committee recommends to the Board of Regents that they amend the By-Laws that in the case of Associates who have prolonged illnesses during which time they can neither study nor work, that that time be eliminated from the five-year term and time be extended; also that Dr. Mackay benefit thereby, as provided.

"The Committee realizes that this requires a change in the By-Laws. It is eager to do everything it can for Dr. Mackay but sees no way to extend his term until the By-Laws are changed.

"Application for reinstatement: The Committee recommends to the Board of Regents the reinstatement to Fellowship of Dr. Konrad Birkhaug, Albany, N. Y."

(On motion by Dr. Pincoffs, seconded by Dr. Morgan, and regularly carried, Dr. Konrad Birkhaug was reinstated to Fellowship.)

Continuing Report of Committee on Credentials:

"New Business—

"(*a*) The Board of Regents on October 20, 1946, adopted a resolution directing that the Credentials Committee review the routine of using the inquiry card system on candidates for Fellowship and Associateship and report back to the Regents. In reviewing the By-Laws of the College, Article V, Section 2, provide, in part, 'further, the name of the candidate (for Fellowship) shall be sent to each Fellow in the candidate's locality, with a request for comments as to the candidate's fitness.' The By-Laws make no such stipulation with regard to the candidates for Associateship, although it has been the custom to use the inquiry cards for Fellow and Associate candidates alike.

"The College membership has grown so great that the card system has become top heavy, requiring, in some instances, up to three hundred cards for a single candidate with consequent great expenditure of labor, materials and postage, and with the growing number of cards it becomes the more difficult and time-consuming to pass on the credentials of each candidate. The Committee considered several possible substitutes, and is now ready to recommend to the Board of Regents the discontinuance of the individual inquiry card system, and to substitute in its place the publication of a printed list of all candidates, to be distributed to Fellows and Masters of the College adequately in advance of each Credentials Committee meeting, thus giving every Fellow or Master an opportunity to vote for or against any candidate. The Committee further recommends that all proposals shall be required to be filed sixty days in advance of the Committee meeting, thus giving the Executive Offices adequate time to publish and distribute the lists and to receive the votes.

"This recommendation, in the opinion of the Credentials Committee, will be more effective and more economical, and will not require any change in the present By-Laws, in view of the fact that the By-Laws do not specify in what manner the names of candidates shall be submitted to the Fellows and Masters of the College."

In discussing this matter Dr. Piersol pointed out that this published list will go to all Fellows of the College in one general mailing and that the names will be arranged geographically for easy reference. It will be required that each proposal be filed at least 60 days before the meeting of the Credentials Committee; the published list will

be mailed during the 60-day interim. No names will be included on the list unless the proposal is filed with the Executive Offices as specified. This will eliminate the last-minute going over of certain additional names, which happens every year, and which is most unsatisfactory and probably unnecessary. It is due largely to oversight on the part of sponsors and, in some instances, to lack of attention of the Governor. This recommendation has been the result of much discussion and is the only solution we have to recommend, he said.

(On motion by Dr. Brower, seconded by Dr. Irons, and regularly carried, this recommendation of the Committee was approved.)

Dr. Piersol, continuing the Report of the Credentials Committee:

"(*b*) Candidates for Fellowship: The following is a summary of the recommendations of the Committee (a list of the recommended candiates for Fellowship has been placed in the hands of all Regents and Governors):

"Recommended for Advancement to Fellowship	102	
Recommended for Direct Election to Fellowship ..	22	124
Recommended for Election first to Associateship		6
Deferred		42
Rejected		10
		182

"It is recorded of the 22 candidates recommended for election directly to Fellowship, 4 were former Associates who previously were dropped for failure to qualify but were given credit for their Associate terms, and who now have presented adequate and satisfactory credentials for Fellowship.

"The Committee recommends to the Board of Regents the election to Fellowship of the 124 candidates on this list." (This list of 124 candidates has been combined with the list recommended for election at the meeting on April 27, 1947, and has been published in the May, 1947, issue of this journal.)

(On motion by Dr. Piersol, seconded, and regularly carried, the candidates (124) on the list were formally elected to Fellowship.)

Dr. Piersol, continuing the Report:

"(*c*) Candidates for Associateship: The following is a summary of the recommendations of the Committee (a list of the recommended candidates for Associateship has been placed in the hands of all Regents and Governors):

"Recommended for Election to Associateship	194	
*Fellowship Candidates Recommended for Election First to Associateship	6	200
Deferred		44
Rejected		25
		263
	* plus	6

"The Committee recommends to the Board of Regents the election to Associateship of the 200 candidates on this list." (This list of 200 candidates has been combined with the list recommended for election at the meeting on April 27, 1947, and has been published in the May, 1947, issue of this journal.)

(On motion by Dr. Morgan, seconded by Dr. Tenney, and regularly carried, the group of 200 candidates was elected to Associateship.)

Dr. Piersol, continuing his Report:

"The Committee on Credentials again met this morning, with all members present, and considered an additional list of candidates. The meeting ended only a few minutes before the meeting of the Board of Regents began and, therefore, there has been no opportunity to type the prepared list, so we shall have to read the names to you.

"The following is a suummary of candidates for Fellowship:

Recommended for Advancement to Fellowship	25	
Recommended for Direct Election to Fellowship	9	34
*Recommended for Election First to Associateship		4
Deferred		23
Rejected		3
		64

"The Committee recommends the election of the following 34 candidates to Fellowship." (Reads the list, which has been combined in these Minutes with the list of Fellows previously elected and published in the May, 1947, issue of this journal.)

(On motion by Dr. Lee, seconded by Dr. Morgan, and carried, the 34 candidates were formally elected to Fellowship.)

Dr. Piersol, continuing his Report:

"Candidates for Associateship: The following is a summary of the recommendations of the Committee:

Recommended for Election to Associateship	66	
*Fellowship Candidates Recommended for Election First to Associateship	4	70
Deferred		18
Rejected		10
		94
	* plus	4

"The Committee on Credentials recommends to the Board of Regents the election of the 70 candidates to Associateship." (Reads the list of names, which have been combined with the list of Associates previously elected at this meeting and published in the May, 1947, issue of this journal.)

(On motion by Dr. Paullin, regularly seconded, and carried, the 70 candidates were formally elected to Associateship.)

Dr. Piersol left the meeting and on request of President Barr, Dr. Sloan continued the report:

"The Committee, after due deliberation, recommends to the Board of Regents election to Mastership in the College of the following:

"Dr. Ernest B. Bradley	Lexington, Ky.
Dr. Sydney R. Miller	Baltimore, Md.
Dr. John H. Musser	New Orleans, La.
Dr. George Morris Piersol	Philadelphia, Pa.

"They are all past Presidents of the College, former members of the Credentials Committee, and men who have performed signal service for the College over many years. Dr. Bradley, Dr. Miller and Dr. Musser are incapacitated and are unable to accept their Masterships in person. How-

ever, in their absence, Dr. Ernest E. Irons will act for Dr. Bradley; Dr. William S. Middleton for Dr. Musser; and Dr. Wetherbee Fort for Dr. Miller."

(On motion by Dr. Paullin, seconded by Dr. Stroud, and regularly carried, the above four physicians were elected to Mastership and the recommendation of the Committee on Credentials approved.)

Dr. Roger Lee, Chairman of the Committee on Public Relations, presented a report dealing with numerous communications, resignations and some fees and dues cases. Several of the communications were in regard to possible action by the College in inspecting hospitals and matters of that sort. The general action of the Committee was to report that the American College of Surgeons, whose hospital experts inspect hospitals, and the American Medical Association, through its Council on Medical Education and Hospitals, are at present the official agencies to inspect hospitals for internships and residencies, and to report that The American College of Physicians does not engage in this activity, other than to participate informally with the Council on Medical Education and Hospitals.

On recommendation of the Committee on Public Relations, the resignation of Dr. Robert E. Lyons, Jr. (Associate), Bloomington, Indiana, was accepted. Likewise, in accordance with the recommendations of the Committee, the dues of nine members who are ill and at least temporarily out of practice were waived for the current year and until recovery and resumption of practice.

Report, House Committee, Dr. William D. Stroud, Chairman: "A special meeting of the House Committee was held at the College Headquarters, Philadelphia, on Friday, April 18, with all members present—Dr. Charles L. Brown, Dr. T. Grier Miller, and Dr. William D. Stroud, Chairman.

"In accordance with directions and approval of the Board of Regents at its last meeting, October 20, 1946, the following improvements, within the appropriations, have been completed, inspected and approved by the Committee:

"(1) a kitchen has been installed on the third floor for the use of the caretakers, and the former basement kitchen has been converted into a machine room for the Addressograph Department;

"(2) doors, perfectly matching in design the original doors in the building, were installed on the second floor between the Assistant Executive Secretary's general office and private office;

"(3) four rooms on the upper floors have been renovated and repapered.

"At the last meeting of the Board of Regents, the House Committee was instructed to determine the cost of preparing drawings and specifications for the proposed new addition to the College Building and to further explore the possibilities and cost of building. The Committee has consulted two different architects, including the Trumbauer firm, who were the original architects and building supervisors of the College Headquarters. That firm obviously is thoroughly familiar with every detail of the present building, and one of its officers, Mr. Frank, without obligation to the College and without charge, prepared floor plans and an elevation drawing of the building as it would appear with the proposed extension, said plans and drawings being in my hands for display.

"The Trumbauer firm will prepare plans, specifications, detailed drawings and supervision for the proposed addition for a fee of 6% of the total cost of the work, payments to the architect to be as follows:

"(1) upon completion of the preliminary studies, one-fifth of the total architect's fee would be payable;

"(2) upon completion of specifications and general working drawings, two-thirds of the architect's fee will be payable;

"(3) the balance is payable from time to time during execution of the work, and in proportion to the amount of services rendered by the architect.

"The Trumbauer firm states that the cubical content of the new addition is 39,000 cubic feet, and the approximate cost would be $48,000.00 (Incidentally, they told us the name of the builder of the present property between 1904 and 1905, at which time the cost was $50,627.61.)

"The Trumbauer firm furthermore states that in their opinion all materials needed for the addition are readily available, that they feel that building costs of this character are more or less stabilized and would cost no more during the coming year than if delayed for a longer time, say of two years. The only item not available at the present, nor in the future, are bricks of the same length as used in the old building. These no longer are made, but bricks of the same color and thickness are still made, and it is for this reason, the different length of the bricks, that the Trumbauer firm designs the addition with a backset of some eleven feet, which would eliminate any noticeable change in appearance. Furthermore, the Committee, on inspection, believes the designed addition more appropriate for many reasons, than a straight extension of the present building, and points out that the design is in keeping with present architectural policies.

"The other architect consulted quoted a fee of 10% of the total cost of the addition, and estimated its cost at $80,000.00. The Committee is inclined to believe that the Trumbauer firm, from its own first-hand experience with designing and supervising the construction of the original building, is in a far better position to estimate the cost of the proposed addition. Obviously, there is a wide difference between the two architects' fees—one based on 6% of $48,000.00, or $2,880.00, and the other based on 10% of $80,000.00, or $8,000.00.

"The Committee unanimously voted to recommend to the Board of Regents at this meeting the approval of the preliminary plans submitted by the Trumbauer firm; the official employment of the Trumbauer firm; the authorization of the Committee to request the Trumbauer firm to obtain two bona fide builders' quotations; and such other authorization to the House Committee and the Executive Committee to proceed in accordance with action taken at this meeting by the Board of Regents."

(On motion by Dr. Irons, seconded by Dr. Lee, and regularly carried, the above report was accepted. It was pointed out that the carrying out of the program would be under the direction of the Executive Committee and the House Committee.)

Adjournment, 5:00 p.m.

Attest: E. R. LOVELAND,
Secretary

ABRIDGED MINUTES, BOARD OF REGENTS

SECOND MEETING

CHICAGO, ILL.

APRIL 29, 1947

The second meeting of the Board of Regents during the 28th Annual Session of The American College of Physicians convened at 12:30 o'clock, April 29, 1947, at the Palmer House, Chicago, with Dr. David P. Barr presiding, Mr. E. R. Loveland acting as Secretary, and the following in attendance:

David P. Barr	*President*
Hugh J. Morgan	*President-Elect*
James J. Waring	*1st Vice President*
A. B. Brower	*2nd Vice President*
T. Homer Coffen	*3rd Vice President*
William D. Stroud	*Treasurer*
George Morris Piersol	*Secretary General*
Maurice C. Pincoffs	*Editor*
Chauncey W. Dowden	*Chairman, Board of Governors*
E. L. Bortz	*Chairman, Advisory Committee on Postgraduate Courses of the Board of Governors*

Francis G. Blake
James F. Churchill
Reginald Fitz
Roger I. Lee
Charles T. Stone
Walter B. Martin
William S. Middleton
James E. Paullin
LeRoy H. Sloan
George F. Strong
Ernest E. Irons
T. Grier Miller
Charles F. Moffatt
Charles F. Tenney

The Secretary read abstracted minutes of the previous meeting. The Secretary presented the following communications:

(1) A letter from Dr. Archie M. Palmer, Director of the Patent Policy Survey Committee of the National Research Council, asking if The American College of Physicians has given consideration in its program or in its publications to the question of University Patent Policies and expressing his interest in discovering all available material on the subject, as well as research by educational and professional groups. The matter was opened for discussion.

DR. PINCOFFS: There appeared in the ANNALS about 10 years ago an editorial on this subject. It cannot be taken as an official statement of the College, however. At the time, there was a tendency to subsidize laboratories and there was a rather confused situation as to whom the results of the work belonged. The editorial tried to point out the dangers as well as the advantages, but it did not attempt to state the policy of the College. There is as yet no College policy as regards this question.

DR. LEE: This is a real controversial subject. People feel very strongly about it; threats of law suits are frequent. This should be referred to the Committee on Public Relations. It cannot be settled very simply or easily by the Regents.

PRESIDENT BARR: This communication will be referred to the Committee on Public Relations for consideration and report.

Communications Continued:

(2) A letter, in two parts, from Dr. LeRoy H. Sloan, suggesting to the Board of Regents that on alternate years the College holds its meeting in an area which is not especially able to handle clinical meetings, and stating that he felt it a mistake to center the College meetings in purely clinical areas. By having alternate meetings clinical in nature and the intervening meet-

ings concentrated on morning lectures, panel discussions, and general sessions, Dr. Sloan felt that a wider selection of meeting places would be available and that the general interest of the College would be adequately or better served. The second suggestion was that the personnel of the Committee on Credentials be withheld from publication.

The discussion of the character of Annual Meetings was deferred for the third meeting of the Board of Regents, but the matter of the publication of the personnel on the Committee on Credentials was generally discussed. It was determined, by resolution, not to withhold the personnel of the Committee on Credentials from publication.

PRESIDENT BARR: May we now have the report of the Committee on the Annals of Internal Medicine, Dr. Fitz, Chairman.

DR. FITZ: The Committee reports that the ANNALS has had a successful year. The subscriptions have increased steadily, showing how popular is our editorial policy. Our financial health is blooming, almost in a manner that is pathological.

In 1932, there were 1,800 subscribers, in contrast to 10,000 for April, 1947. During 1946, $28,146.00 was added to the general fund of the College from the operation of our periodical.

It must be emphasized, however, that these figures, besides revealing expert editorial management, also reflect abnormal times, for we have faced a continued paper shortage which has made it impossible to print as many pages and in as extensive a fashion as we would like. During January, February, and March of this year, 488 pages of reading material were printed, in contrast to 628 pages during the corresponding months in 1941. This means that the selection of material to be published has been chosen with most punctilious care, but, to offset that, a number of desirable articles either have been delayed in publication or have been rejected—a fact causing a certain amount of complaint and irritation in the minds of prospective contributors.

The cost of printing the ANNALS is increasing. Therefore, it seems reasonable to predict that our financial record will be far less spectacular when the journal regains its normal and desired size.

The Committee feels that the Editor's policies are wise. Last year an exceptional proportion of well-written and informative articles appeared, so that the method of their selection and the manner in which they have been edited have been admirable. The editorials have been instructive and have expressed a sound point of view. We now have about eighty exchanges, chiefly with medical periodicals published outside of North America. The establishment of a limited number of such exchanges, we believe, is important from the viewpoint of public relations and already has made many new friends for the College.

The Committee has discussed with the Editor the affairs of the ANNALS. The present salary levels and the cost of operation are satisfactory. As the journal enlarges, however, new problems are certain to arise. The office space occupied by the Editor is already in need of expansion, and a number of new developments are under consideration—developments such as the possibility of a more elaborate book review department, or entering the field of abstracting current articles of importance which appear in other medical periodicals, or of developing annual reviews on topics of general interest. Such matters lie in the future. At present, the Committee can only reiterate its pleasure in having the Editor back at his desk and its confidence in his wisdom and skill.

(On motion seconded and regularly carried, the above report was accepted.)

PRESIDENT BARR: You will next hear from the Editor, Dr. Pincoffs.

DR. PINCOFFS: Mr. President, Members of the Board of Regents: The Editor has nothing to add. He feels that he has been very handsomely dealt with in the preceding report.

I would like, however, to obtain expressions from the Board of Regents concerning the use of the Editorial section of the ANNALS as a medium for making public the policy of the College in questions of general interest to our membership.

At present the Editorial section is utilized chiefly to present brief topical reviews of recent work in the field of internal medicine. These are entitled Editorials and, judging by the requests received for reprints, they are popular with our readers.

Occasionally I have written editorials reviewing trends in medicine or in medical education. Occasionally in the past I have written editorials on controversial subjects such as the subsidization of medical research by industry or the certification of specialists, this last prior to the approval by the College of the principle of certification.

It is in regard to this last mentioned type of editorial, that which expresses the opinion of the Editor on a controversial subject in relation to which the College has no fixed policy, that I wish the opinion of the Regents.

As I now view this question, the Editor should not publish editorials on matters of policy without authorization from the governing bodies of the College since unescapably such editorials in the official College publication will be taken to express not the Editor's personal opinion but the College policy.

Personally I should like to see the College more active in developing its influence in the profession by formulating its approval or disapproval of many developments in the broad field of medical care which are subjects of controversy. I should like to see the Editorial section of the Annals utilized to make public the attitude of the College in these debatable questions.

Since at present the College has not organized itself to study such questions nor to exert its potential influence in determining their decision, I feel that an appropriate rule for the Editor to follow is to limit publication of editorials on questions of policy to such as have received the approval of the President and perhaps of the Board of Regents. I would appreciate expressions of opinion on this subject.

PRESIDENT BARR: This subject is open for discussion.

DR. FITZ: Would it not be possible to suggest, relating to editorials on matters which might be very much in the public mind and debatable, that the Editor adopt, as a matter of policy, the idea of submitting any proposed editorial to all the other members of the Editorial Board and to the President, and be guided by the editorial opinion of that group before publishing such an editorial as he might have in mind?

PRESIDENT BARR: It seems to me that we already have a system which Dr. Pincoffs has in mind which can be put into effect without any more formality than that.

We will now have a report from the Conference Committee on Graduate Training in Medicine by the Chairman, Dr. Fitz.

DR. FITZ: In December, 1939, the Regents established a special committee of two to confer with the American Board of Internal Medicine and the Council on Medical Education and Hospitals of the American Medical Association. The aim of this Committee was twofold: To play a part in the work of hospital inspections so that residencies in medicine approved by the Council would meet with the approval of the Board and the College, and to serve as a source of information to the Regents in regard to various programs in the training of internists that might be established in medical schools or hospitals.

The Committee has not been inactive. The first problem it approached was that of developing a mechanism by which hospitals approved for resident training in medicine by the American Medical Association should also be approved by the Board of Internal Medicine and the College. When the Board first came into existence, considerable dissatisfaction was manifest. It was generally believed that many residencies in medicine approved by the Council were by no means approvable by the Board or the College and that, therefore, some uniform method of inspection and classification was desirable. This difficulty was surmounted by a simple agreement. The

Council agreed no longer to list residencies in medicine as approved unless they were also approved by the Board and the College. The machinery for inspection developed by the Council was not interfered with but the report of hospital inspections was sent to the Board and to the Conference Committee. Since that agreement was reached, no hospital residencies in medicine have been listed as approved by the Council unless they had also Board and College approval.

The War delayed the complete development of this program and necessitated a new and temporary makeshift. As the demand for resident training in medicine grew, many hospitals hitherto uninterested in education seemed to wish to play a part. The Council could not keep up with inspections at the rate the hospitals demanded and a large backlog accumulated which consisted of hospitals with residencies approved many years before and not recently re-inspected. An attempt was made to bypass some of these difficulties by the expedient of "temporary approval." Certain residencies in medicine that were guaranteed as being of adequate educational value by sources which the Committee and the Council and the Board regarded as reliable, were given "temporary approval." This method of getting work done has proved helpful. It must be emphasized, however, that such approval is only temporarily valid and may be denied when more formal inspections are made.

As the postwar program of residency training again becomes stabilized, the original plan should be resumed. A fair and accurate evaluation of the educational worth of any medical residency is essential. This is better obtained by the combined judgment of three such responsible agencies as the College, the Board, and the Council working together than by any one of these agencies working alone.

The Committee asks that this report be accepted as a report of progress. I move the existence of the Conference Committee continue for at least another year; its members being appointed by the President.

(The motion was seconded and opened for discussion.)

MR. LOVELAND: When this Conference Committee was first initiated, there were two members from the American Board of Internal Medicine and two members from the Board of Regents of The American College of Physicians for the purpose of sitting in with the Council on Medical Education and Hospitals at its meetings to review its inspectors' reports and finally to decide on whether a hospital shall be approved for resident training. The late Dr. Cutler, then Chairman of the Council, worked out a scheme by which the American Medical Association would use its machinery for the inspection of hospitals and the assembling of data, later to be considered at a joint meeting of the Council and the Conference Committee for action. This plan grew out of numerous requests coming to the College, asking the College to initiate a hospital inspection system comparable to that of the American College of Surgeons. It was the opinion of the Board of Regents of this College that a separate and additional certifying agency would duplicate in large part the work of the Council and that, therefore, the College should show its cooperative interest by participating with the Council through this Conference Committee. It was felt that such a plan would coordinate the standards and the objectives of the Council, the American Board and the College of Physicians.

DR. SLOAN: I would like to say that this technic is not in use at the present time.

MR. LOVELAND: No, Dr. Cutler's death and the War interrupted the consummation of the plan. Some of our Board will recall that back in the early 40's several members of our Board of Regents held a joint meeting with the Board of Trustees of the American Medical Association to discuss this whole matter, and thereafter, in numerous conferences with Dr. Cutler, the proposed plan was worked out.

DR. IRONS: When that matter was taken up, I was Chairman of the American Board of Internal Medicine. We found it difficult to get much action out of a Com-

mittee, even of six, and so the Conference Committee of six delegated to a representative of each group the duty of coming to a friendly agreement as to what should be done. Dr. Cutler, Dr. Hugh Morgan and I constituted that Committee. We obtained a very friendly working arrangement, with the Council being the inspecting agent. That was followed in the case of many, many hospitals which were inspected by the Council and passed on with the assistance of our Committee. Then came the War, Dr. Morgan was away, and I was no longer the Chairman of the Board. Dr. Cutler had died and, in the meantime, the record has been pretty well obliterated. I think your plan, Dr. Fitz, would be a very good one and probably you could reinitiate that close coöperative arrangement among representatives of the Board and of the College and of the Council.

DR. WARING: The present situation concerning recognition of hospitals for residencies is quite confusing. The Council on Medical Education has given a number of hospitals temporary approval pending the opportunity later to complete full inspection and appraisal. I feel that in some way we should be able to appraise this type of training more accurately, especially in view of the fact that our requirements are changing. The Board is not going to adhere rigidly to the old three-year period of graduate training and two years of practice, but is permitting substitution of certain things that take a little more time. This will recognize the importance of the experience that a young man is going to get in private practice, especially if he is under the tutelage of a competent, older man.

(The motion was put to a vote and carried.)

PRESIDENT BARR: The next Committee report is that on Fellowships and Awards by the Chairman, Dr. Fitz.

DR. FITZ: This report is divided into three distinct parts.

As has already been announced, the Committee has selected Dr. Fuller Albright of Boston as this year's recipient of the John Phillips Memorial Award.

Under special authority of the Board of Regents, the Committee has awarded five new Research Fellowships for the ensuing year, to wit:

(1) Ward S. Fowler, 31 years old, a graduate of Harvard, who is to work on the pathologic physiology of certain pulmonary diseases at the Graduate School of Medicine, University of Pennsylvania.

(2) Arnold L. Johnson, 33 years old, a graduate of McGill in 1940, who is to work on the hemodynamics of congenital heart disease at the Children's Memorial Hospital in Montreal.

(3) Mary Ann Payne, 33 years old, a graduate of Cornell in 1945, who is to work on hepato-renal problems in shock and hypertension at the New York Hospital.

(4) Miriam M. Pennoyer, 32 years old, a graduate of Rochester Medical School, who is to work in St. Louis on the function of the adrenal glands in the newborn.

(5) Philip F. Wagley, 29 years old, a graduate of Johns Hopkins, who is to study certain mechanisms in hemolysis at the Thorndike Memorial Laboratory in Boston.

To this list should be added the name of Dr. Tom Fite Paine, Jr., who is to continue a Fellowship awarded a year ago so that he may further his studies in infectious diseases at the Thorndike Memorial Laboratory, where he is working with Dr. Maxwell Finland.

The Committee has reviewed the records of those who have received Clinical or Research Fellowships from the College. We are convinced that not only have such Fellows successfully promoted and advanced clinical research through oppor-

tunities opened to them by the College, but have also helped to maintain our high standards. Therefore, we believe that these Fellowships are an important College activity.

A review of the 1946–1947 record is as follows: Ten Clinical Fellowships were awarded and three Research Fellowships; a total sum of $32,000.00 being allocated for their establishment. Of the Clinical Fellowships, three have been completed, four are still active, to end between June and November, and three of our Fellows resigned before completing their term of service. Of the three Research Fellowships, one has been completed, one is still active, to end in September, 1947, and one was not accepted. Of the total $32,000.00 which might have been spent, $5,667.00 has been unexpended.

On the 20th of October, the Board of Regents appropriated $20,000.00 to guarantee not more than eight Research Fellowships for the ensuing year. The Committee has voted to expend only $15,400.00 of this sum and to recommend that the residual unexpended $4,600.00 be set aside in a special Fellowship Fund to be drawn on at some later date when special needs for Fellowship funds may be more urgent than they happen to be at present.

We are asking that the unexpended sum of $20,000.00 that the Regents have voted to set aside for the purpose, be put aside in a special fund, because we feel at the present moment there are a lot of Research Fellowship funds around that can be obtained, and we believe that can't continue indefinitely, and we would like to suggest that a little fund for the purpose against bad days be built up.

I move the adoption of this part of the report.

(The motion was seconded by Dr. Waring. The question was called for, voted upon, and it was carried.)

Dr. Fitz: The next part of the report deals with the Alfred Stengel Memorial.

At the last meeting of the Board, no plans were proposed for the Alfred Stengel Memorial which Dr. Bruce hoped might be established as part of his legacy. The Committee makes the following recommendation:

There shall be established an award, known as the Alfred Stengel Memorial Award. This shall be awarded periodically by the President at a Convocation of the College to a Fellow—and preferably to a Fellow who has served as an Officer, Regent or Governor—who by virtue of his loyalty and service to the College deserves an honor from it that is unique. Besides loyalty and service to the College, the candidate shall have displayed an outstanding influence in maintaining and advancing the best standards in medical education, medical practice and clinical research, in perpetuating the history and traditions of medicine and medical ethics, and in upholding the dignity and the efficiency of Internal Medicine in its relation to public welfare. In brief, the award shall correspond to an Honorary Degree conferred by the College on those of its Fellows who have seemed most perfectly to have carried forward its aims and Dr. Stengel's ideals.

The recipient each year shall be chosen by the Board of Regents at a regular meeting prior to the Convocation at which the award is to be made. At least three and not more than five nominations shall be presented to the Board of Regents at their meeting at which the matter is to be considered. These nominations shall be made by a special committee appointed for the purpose by the President; it shall include the President and Secretary General ex-officiis, three members of the Board of Governors and two members of the Board of Regents. This Committee may make no nominations if appropriate candidates are not apparent. The Regents may have power of veto if, in their judgment, no one of the proposed candidates in any year is worthy of the proposed honor.

The Board of Regents shall make their selection by secret ballot. On the first ballot the two candidates receiving the greatest number of votes shall be chosen for

final vote. The candidate who finally receives the majority of votes shall be the recipient of the award at the next Convocation. No award shall be made unless the candidate thus selected is present to receive it. No announcement shall be made as to the name of the recipient so elected until after the award has been made.

The award shall be in the form of a diploma. This shall be designed by a Committee of three appointed by the President. The cost of its preparation shall be borne by the Bruce Fund.

The Committee recommends that that plan be established for the Alfred Stengel Memorial Award.

(The motion was seconded by Dr. Blake, was put to a vote, and was carried.)

DR. FITZ: The third matter is as follows:

The Committee has considered carefully how the residual income of the Bruce Fund—representing approximately $200.00 per year—can best be spent. The following recommendation is made:

> That until otherwise ordered, such income shall be added each year by the Treasurer to the sum appropriated by the Regents for Research Fellowships;
>
> That each year the Committee on Fellowships and Awards shall select from the Research Fellows nominated the one who in their judgment offers greatest promise of attaining unusual distinction in investigation, teaching and as a clinician; and
>
> That such Research Fellow shall be designated as the "Alfred Stengel Research Fellow of The American College of Physicians", stipend being paid in part from the income of the Bruce Fund.

I move the adoption of this recommendation.

(The motion was seconded by Dr. Lee, was put to a vote, and was carried.)

DR. FITZ: I move the adoption of the report as a whole, if that is possible.

PRESIDENT BARR: If there is no objection, the report will be adopted.

We will next have the report from the Committee on Finance, Dr. Charles Tenney, Chairman.

DR. TENNEY: The Committee on Finance met on April 28, 1947, with Dr. Charles T. Stone, Dr. Roger I. Lee, and the Chairman, Dr. Charles F. Tenney present, and with the Treasurer, Dr. William D. Stroud, and the Executive Secretary, Mr. Loveland, sitting in.

The Committee reviewed the Auditor's reports of College operations for 1946, copies of which are being distributed to the Board of Regents. Salient points include the following:

(*a*) The Endowment Fund increased $27,177.05, to $223,373.89; the General Fund increased $8,880.82, to $234,159.26; total of both Funds, December 31, 1946, $457,533.15;

(*b*) Life Membership Fees for 1946 amounted to $28,495.15; there was a realized profit on investments of $1,981.90, and there was an addition of the James D. Bruce Memorial Fund of $10,000.00;

(*c*) The total income for the year was $152,058.08; total expenses, $138,072.17, leaving a balance of $13,985.91; add to this the accrued interest on securities to December 31, 1946, $1,552.91, and the net income of the General Fund amounts to $15,538.82.

Detailed financial statements prepared by the Auditor and already in your hands will provide all information you may desire, and contain a certified registry of all investments.

The Investment Counsel report of February 26, 1947, discloses the following:

	Endowment Fund	*General Fund*	*Total*
Market Value	$238,958.75	$150,291.25	$389,250.00
Book Value	229,261.74	147,538.28	376,800.02
Appreciation			$ 12,449.98

The Finance Committee herewith reports to the Board of Regents the following additional purchases of securities for the Endowment Fund since January 1, 1947, and asks the approval of the Board of Regents. These purchases were made from available balances in the cash account of the Endowment Fund, and were approved by the Finance Committee, upon recommendation of our Investment Counsel:

10,000 United States Savings Bonds, Series "G", 2½'s	$10,000.00
100 Shares, American Gas & Electric Co., common	4,035.03
100 Shares, Buffalo Niagara Electric, $3.60, pfd.	10,185.00
	$24,220.03

The Committee has recommended to the Treasurer that we request the Investment Counsel, Drexel & Co., to have the College securities analyzed by a different individual from time to time, thus to get the benefit of new thought and analysis.

The Investment Counsel has requested the consideration of increasing their fee from $200.00 to $400.00 annually, but in view of the fact that actually the College investment portfolio has merely grown in volume of dollars, but not materially in the number of different securities, the Committee feels that it would be adequate if their fee were not increased more than $100.00, instead of $200.00, and has directed the Treasurer to consult them (Drexel & Co.) concerning this.

On recommendation of the Investment Counsel, dated April 18, 1947, the following investment changes are recommended, subject to the approval of the Board of Regents, since the accounts affect the Endowment Fund:

Sale

5,000 Chicago and Western Indiana RR Co., Consolidated, 4's, 1952, at approximately 107;

Purchase

50 Shares, Atlantic Refining Co., $3.75, pfd.;
20 Shares, Liggett and Myers, common,

and the balance to be invested in U. S. Savings Bonds, series "G", 2½'s. These purchases include the investment not only of the proceeds of the balance from the Chicago and Western Bond, but also approximately $6,800.00 cash balance now in the Endowment Fund.

The Committee is in receipt of notification from the Investment Counsel that we have received 100 Shares, Houston Light and Power Co., common, due to a two-for-one split of our holdings in that security—this being paid as a stock dividend.

The Committee recommends to the Board of Regents an additional appropriation of $200.00, to be added to the President's budget for the current year.

The income of the College since January first of the current year has materially increased from dues and Life Membership subscriptions. Already some $48,000.00 has been collected from dues and $21,000.00 from Life Membership subscriptions. These exceed considerably our estimated income prepared last autumn. The Committee reports to the Board of Regents that the present balance in the General Fund is adequate to cover the building program, should the Executive Committee go forward with it, without disturbing any investments of the College.

PRESIDENT BARR: You have heard Dr. Tenney's report. Is there a motion to adopt it?

DR. IRONS: I would like to say that this is a most excellent report, and no question could be raised in criticism of it. Also the expenditure for Fellowships is highly desirable because the College has educational activities as its principal function. I think I remember, though, that here about a year ago when the appropriation of $32,000.00 was made for Fellowships, that this total amount exceeded the visible receipts as estimated for the coming year. I wonder if that was a good act? Fortunately, there were receipts which were unexpected and, therefore, no deficit developed.

I speak of these things because I have just been through another period in another organization, the American Medical Association, where there was the same kind of situation, only in a little larger amounts. Both organizations are eminently sound financially. It is just a question of policy. I know that to raise such a question is not a very popular thing to do, but I think the Board ought to think of that side of it. No budget should be passed which does not come within the prospective income.

One other matter, the College is an expanding and rapidly growing institution. There are now over 6,100 members. Whenever an organization or business grows, its financial obligations increase and, consequently, it needs an increase in its available quick assets, and also in its working capital. That is a general, recognized principle. Now, we have, it is true, a very pleasant financial report, due to the care of the Finance Committee and the Treasurer. But it seems to me that it might be a good plan if you could prepare a little for the coming depression, which is bound to hit us. There is no mechanism that has ever been devised to prevent this up and down movement of business. Our business must go on whether there is a depression or not. We ought to build up some reserve to meet such a contingency, which will surely arise.

As a beginning of that, I wonder if it would not be wise to have set up a reserve fund? At present you could call it a Building Reserve. Of course, we would spend it if things go right, but we might set up a Building Fund for $50,000.00, and name another reserve a little later, so that we don't have so much free money; and don't put it in the Endowment Fund, but keep it more for liquid use, at the discretion of this Board.

I know that it is just bookkeeping, putting it from one pocket to another, but it does have a very restraining and favorable effect on the attitude of spending bodies, when some of these funds are put away with a little bit of an earmark.

(Upon motion regularly made, seconded, and carried, the report of the Committee on Finance was accepted.)

PRESIDENT BARR: May we now have the report of the Advisory Committee on Postgraduate Courses, Dr. E. L. Bortz, Chairman.

Dr. Bortz spoke at some length on the objectives of the Advisory Committee on Postgraduate Courses and outlined the courses proposed on the schedule for the autumn of 1947 and some of the courses on later schedules for 1948. He brought up for discussion the matter of the matriculation fee for the courses. Previously, the standard fee in the College had been $20 for members and $40 for non-members. In comparison with fees charged by various medical schools and institutions, the College fees were thought to be quite too low. Therefore, the Committee recommended that the fee be increased to $30 per week for members, $25 of which shall go to the Director of the course and the institution and $5 of which shall be retained by the College to help cover administrative expenses. Dr. Bortz further stated that the Committee is interested in broadening the basis of training in these courses and will add more and more basic science data to the content thereof. He stated also that many other medical bodies and groups of higher learning in specialized fields have consulted the College concerning the manner in which our program is conducted and, in many instances, have copied in large measure our whole plan of instruction. He said that

the Committee is somewhat disturbed by the fact that there is such a demand for the courses that the College is unable to accommodate many. He said also that the Committee favors the reduction in the size of the classes to 25 or 30 physicians and that it has been due only to the pressure of registrants that classes temporarily have been very much larger in many instances. The Committee has continued to receive the active and enthusiastic support of the various faculties of medicine over the country and also offers, from time to time, from institutions that wish to participate. Dr. Bortz said it appears there is a certain amount of recognition that is bestowed upon the directors and the institutions selected for the College courses and that the reaction is quite favorable. The letters and reports from those who take the courses have been very helpful for the guidance of the Committee in improving and extending its program. These reports are summarized and offered to the Directors for further improvement in their particular courses.

Dr. Bortz' report was accepted by the Board of Regents.

PRESIDENT BARR: May we have a further report from the American Board of Internal Medicine through its Chairman, Dr. Waring.

DR. WARING: To finish up my unexpired term of two years, the American Board submits to your wisdom the following list of names:

Dr. Walter L. Palmer	Chicago, Ill.
Dr. Chester M. Jones	Boston, Mass.
Dr. Henry M. Thomas, Jr.	Baltimore, Md.
Dr. Frank B. Kelly	Chicago, Ill.
Dr. George R. Herrmann	Galveston, Texas

One of these should be selected to fill my unexpired term. Then the Board would like to recommend that Dr. William S. McCann be reëlected for a term of three years; Dr. William B. Porter and Dr. Cecil J. Watson each be reëlected for a term of three years. Dr. McCann is the newly elected Chairman of the Board. Dr. Hugh Morgan is the newly elected Vice-Chairman of the Board. All these elections should start on July 1, 1947.

(On motion by Dr. Fitz, seconded by Dr. Tenney and unanimously carried, Dr. McCann, Dr. Porter and Dr. Watson were re-nominated for a term of three years, beginning July 1, 1947.)

(The Secretary was instructed to conduct a written, secret ballot for the election of the successor to Dr. Waring and after the ballots were counted, Dr. Walter L. Palmer was declared nominated to fill Dr. Waring's unexpired term.)

Dr. A. B. Brower, 2nd Vice President, temporarily assumed the Chair and called for a report from the Committee on Educational Policy.

DR. MIDDLETON: The Committee on Educational Policy met with the Advisory Committee on Postgraduate Courses and agreed in principle in all matters there considered, and, therefore, has no separate report to render.

CHAIRMAN BROWER: Dr. Irons, you have a report on the Joint Committee for Coördinating Medical Services.

DR. IRONS: This Joint Committee was originally organized as a war-time measure under the Chairmanship of Dr. Roger Lee and it was his organizing ability that gave it its good start. The membership was first confined to The American College of Physicians, the American College of Surgeons, and the American Medical Association. It then became evident that it would be helpful to get a wider representation and so from time to time other organizations were added, including the Army, Navy, Public

Health Service, Veterans Administration, the American Red Cross, the Council on Medical Education, the Committee on Rural Medical Service, the Pharmaceutical Association, the Committee on Economics, the Federal Security Agency, the Association of American Medical Colleges, the Federation of State Medical Boards and the Advisory Board on Medical Specialties. Meetings were continued during the War and at the close of the War, it was decided to continue the organization as a sort of forum for American medicine where any question could be discussed and opinions elicited, having in mind that this Committee has absolutely no elective function, but is merely an exploring agency to observe and comment and to influence public opinion. Under this program a number of matters have been considered, such as the organization of the Veterans Administration, Surplus Property Disposal, Red Cross Blood Service, residency opportunities for returning veterans—there are some 10,000 residencies available now, where there were formerly only about 5,000—the distribution of medical services over the nation, the re-organization of the medical departments of the Army and Navy. All of these problems have come up before the Committee and the minutes are published in the journal of the American Medical Association and rather widely read.

(On motion by Dr. Fitz, seconded and carried, Dr. Irons' report was accepted.)

(President Barr resumed the Chair.)

PRESIDENT BARR: We have received letters from Drs. Ernest Bradley, John Musser, and Sydney Miller, new Masters of the College who are unable to be here because of illness. I think it would be very nice indeed if this Board could send an appropriate message to each of these Masters, and if it is so ordered, I will accept the responsibility of sending appropriate messages on behalf of the Board. If there is no objection, that will be done.

Our Board has been asked on numerous occasions this year to send participants to various UNESCO meetings. I have asked Dr. Waring to represent us at a meeting to be held in Denver.

Since this is the last meeting of the present Board, I would like to express to all my appreciation of the coöperation that I have received from every member of the Board. Thank you very much indeed. (Applause.)

(The meeting adjourned at 3 o'clock.)

Attest: E. R. LOVELAND,
Secretary

ABRIDGED MINUTES, BOARD OF REGENTS

THIRD MEETING

CHICAGO, ILL.

MAY 2, 1947

The third meeting of the Board of Regents of The American College of Physicians during its 28th Annual Session was held at the Palmer House, Chicago, on Friday, May 2, 1947, at 1:00 p.m., with Dr. Hugh J. Morgan, the new President, presiding and with Mr. E. R. Loveland acting as Secretary. The following were in attendance:

Hugh J. Morgan	*President*
Francis G. Blake	*2nd Vice President*
Charles T. Stone	*3rd Vice President*
Walter L. Palmer	
Walter B. Martin	
James E. Paullin	
LeRoy H. Sloan	
George F. Strong	
Ernest E. Irons	
T. Grier Miller	
Charles F. Moffatt	
Charles F. Tenney	
David P. Barr	
A. B. Brower	
Alex. M. Burgess	
Ernest H. Falconer	

Visitors:

James B. Herrick
William J. Kerr

PRESIDENT MORGAN: I am sure all of the members of the Board who have served prior to this meeting would want to welcome to the Board Dr. Alex. M. Burgess, Dr. Ernest H. Falconer, Dr. Cyrus C. Sturgis and the new Chairman of the Board of Governors, Dr. Walter L. Palmer. The minutes of the last meeting have been abstracted and reviewed by the Secretary and myself and there is nothing requiring action of this Board today, and unless there is some objection, we will not have the minutes read.

In accordance with regulations of the Constitution and By-Laws, Dr. George Morris Piersol was reëlected Secretary-General, and Dr. William D. Stroud was reelected Treasurer. The following were formally elected as the Executive Committee of the Board of Regents:

*Hugh J. Morgan
Walter W. Palmer
George Morris Piersol
William D. Stroud
Francis G. Blake
Ernest E. Irons
James E. Paullin
George F. Strong
Charles F. Tenney

Likewise, in accordance with various regulations of the Constitution and By-Laws, or of the Board of Regents, the personnel of all standing Committees was appointed. (The personnel of these Committees has already been published in a preceding issue of this Journal and are not herewith repeated.)

PRESIDENT MORGAN: We shall now proceed to select the 1948 meeting place, dates of the meeting and appointment of the General Chairman.

* Chairman.

(Before receiving the invitations, Mr. Frank Power of the Chicago Convention Bureau extended his thanks to the College for coming to Chicago, stated it had been a pleasure to work with the Officers and the Committees and expressed the hope that the College would return in the not too distant future.)

(Mr. Walter Swanson, Vice President of the San Francisco Convention Bureau, presented an official invitation, delineated the facilities of the city, its Convention Hall, its hospitals, its medical schools, and other agencies, and made guarantees with regard to adequate meeting facilities and hotel rooms. He promised full and complete assistance in arranging all details of the meeting and insuring a successful convention. Numerous questions were asked by Board members, which Mr. Swanson answered and then retired. After general discussion and comparison of the facilities and conditions of a meeting in San Francisco with those earlier presented from New York City, and in discussion with Dr. William J. Kerr and Dr. Ernest H. Falconer, on motion by Dr. Blake, seconded by Dr. Tenney and unanimously adopted, San Francisco was selected for the 1948 session during the period April 19–23, inclusive. Likewise, by resolution, Dr. William J. Kerr and Dr. Ernest H. Falconer were nominated and elected Co-Chairmen of the Session.)

(On motion by Dr. Paullin, duly seconded and carried, the President, General Chairmen, and the Executive Secretary were given full authorization to complete all necessary arrangements in regard to the 1948 Annual Session.)

There was a general discussion by Dr. Paullin concerning the possibility of the College sometime holding its Annual Session in a city which might not have the usual clinic facilities but which could conduct a very excellent meeting with reduced clinics but with an increased program of panel discussions, morning lectures, and general sessions. It was pointed out by Dr. Sloan, General Chairman of the Chicago Session, that some clinicians at the meeting felt that their programs were competing with the morning lectures, which accounted, in some instances, for the small attendance at the clinics. Some felt that the College in its enthusiasm provided too abundant clinic facilities and should not expect every hospital to participate. The increasing popularity of the excellent morning lectures makes the larger clinic facilities unnecessary, although there is a continuing demand for real clinics where patients are shown. Dr. Paullin expressed the hope that an Annual Session of the College might be held in Atlanta in 1949, or later, providing a survey of facilities justified an invitation.

(On motion by Dr. Tenney, seconded by Dr. Irons, and carried, the Board of Regents went on record as expressing the opinion that the inclusion of clinics in the program is not a necessity.)

PRESIDENT MORGAN: Is there any other business to be presented?

DR. BARR: Mr. President, may I present a resolution to the Board?

"RESOLVED, that the Board of Regents of The American College of Physicians expresses its appreciation to Dr. Edward L. Bortz, a distinguished Fellow of this College, for his tireless energy, exceptional ability and broad vision in developing and organizing the Postgraduate Courses conducted so successfully under the auspices of The American College of Physicians.

"Furthermore, the Board of Regents extends to Dr. Bortz its hearty congratulations upon his elevation to the Presidency of the American Medical Association, a well-deserved honor which brings distinction not only to him, but also to The American College of Physicians, that he has served so long and faithfully."

(A motion was regularly made and seconded to adopt the resolution and it was put to a vote and carried.)

Adjournment—2:30 o'clock.

Attest: E. R. LOVELAND,
Secretary

GENERAL BUSINESS MEETING

CHICAGO, ILL.

MAY 1, 1947

The Annual General Business Meeting of The American College of Physicians convened at the Palmer House, Chicago, at 2:15 p.m., May 1, 1947, Dr. David P. Barr, President, presiding. Abstracted minutes of the previous General Business Meeting were read by the Secretary, Mr. E. R. Loveland, and accepted by resolution.

The Treasurer, Dr. William D. Stroud, presented the following Annual Report:

"Mr. President, Fellows and Masters of the College: The College accounts have been audited by a Certified Public Accountant for 1946, and the final report will be published to the members through the pages of the ANNALS OF INTERNAL MEDICINE.

"During the year 1946, the College added to its Endowment Fund $27,177.05, chiefly through Life Memberships, and to the General Fund $8,880.82, or a total of $36,057.87. This brought our assets, as of December 31, 1946, to a total of $457,533.15, of which $223,373.89 represents the Endowment Fund and $234,159.26 represents the General Fund.

"The College operated entirely within its budget for the year. Our investments are carefully watched by our Investment Counselor and the Committee on Finance and are in a favorable condition. As of January 1, 1947, the College held investments at book value, totalling for the Endowment Fund $229,261.74, and for the General Fund, $147,537.28, or a total of $376,799.02. These securities, according to present market value, show an appreciation of $12,449.98.

"The Board of Regents has approved a budget for 1947 calling for an estimated income of $165,700.00 and an estimated expenditure of $162,396.61, leaving an anticipated balance slightly exceeding $3,000.00. It is, however, reasonable to anticipate that with the rapid growth in the circulation of our journal and the marked increase in Life Membership, that the surplus will be materially greater.

Respectfully submitted,

WILLIAM D. STROUD, *Treasurer*"

(The report of the Treasurer was formally accepted by resolution.)

Mr. E. R. Loveland presented the following Annual Report of the Executive Secretary:

"Mr. President, Fellows and Masters: My report is supplementary to those of the Treasurer, the Secretary-General and the President. With the advent of peace, the 35 per cent of our members who were in the Armed Forces have, in very large measure, returned to civilian activities. We are gratified to have them returned to active participation in the College. There has been an enormous increase in the volume of College activities, in the past year; as an illustration, the circulation of the ANNALS OF INTERNAL MEDICINE has grown not only in North America, but throughout the world, until it now has reached 10,000, which is greater than that of any other journal in our field, including those of much greater age.

"Naturally, there has been a great impetus in membership activities and in the number of candidates seeking membership.

"Our Regional Meetings program is now centering around the individual and more personal type of State meeting. Since the last Annual Session, nineteen Regional Meetings have been held in various parts of the United States, with an

attendance representing at least 50 per cent of the College membership. Six of these meetings were of the multi-State character.

"A year ago we proposed to republish the complete Directory of the College, but conditions were such that paper was not available and the costs were prohibitive. Therefore, a new Membership Roster was published as a substitute, until such time as we can revise and publish a full Directory.

"During the past year, Mr. F. V. L. Pindar has been added to the staff of the College as my assistant, and the secretarial staff has been increased.

"We are approaching that time when our present building has insufficient facilities for our work, and the Board of Regents, with the House Committee, is considering plans for an appropriate and adequate addition to our building.

"Those of you who have not yet done so are especially invited to visit the College Booth, where many interesting facts about the College are on display.

"I have just received from our registration desk a report that the total registration at this moment is 4286,* of which 609 are visiting ladies.

Respectfully submitted,

E. R. LOVELAND, *Executive Secretary*"

(The report of the Executive Secretary was accepted by resolution.)

Dr. George Morris Piersol presented the following Annual Report of the Secretary-General:

"Mr. President, Officers, Regents, Masters and Fellows of the College:

"*Membership:* Since the last Annual Session of the College, there have been elected four Masters, 231 Fellows and 396 Associates, which brings the total membership up to 6,179, divided as follows:

8	Masters
4,516	Fellows
1,655	Associates
6,179	Total

"*Life Members:* During the past year, 124 additional Fellows have become Life Members of the College, bringing the total up to 612, of whom 46 are deceased, leaving a balance of 566.

"*Deaths:* It is with regret we report the deaths of 66 Fellows and 10 Associates during this period. Their names have already been recorded in the Archives of the College.

"*Postgraduate Courses:* The Advisory Committee on Postgraduate Courses has been even more active during the past year than heretofore. Through their efforts, there have been organized 23 separate and distinct courses distributed among 22 universities, hospitals and other institutions throughout the country. One thousand twenty-three doctors have taken advantage of these courses, an evidence of their increasing popularity and value.

"*Fellowships:* A further important educational activity of the College has been the creation and extension of Clinical and Research Fellowships. For the calendar year 1946 there was an appropriation of $32,500.00, providing for 10 Clinical Fellowships and three Research Fellowships. For the calendar year 1947, $20,000.00 additional has been appropriated for Research Fellowships. Seven new Fellowships were awarded to begin on July 1, 1947, or shortly thereafter.

* Final registration later recorded, 1,694 members; 1,382 guest physicians; 70 guest non-physicians; 137 senior and graduate students; 518 exhibitors; 609 ladies; total, 4,410.

"As gratifying as are the above mentioned educational activities of the College, it should not be overlooked that the most significant and far-reaching contribution of the College is its Annual Clinical Session. Since their inception, these Sessions have been marked by progressively increased interest and ever widening scope. The present Clinical Session is an outstanding example of what may be accomplished by a year's well coordinated effort. The College is mindful of its great debt to those who have made this Chicago Session possible. Through their example, they have set a pattern to be followed, one which gives assurance of what the future of the College holds in store.

Respectfully submitted,

GEORGE MORRIS PIERSOL,
Secretary-General"

"And now, President Barr, since you assumed office a year ago at Philadelphia, those of us whose privilege it has been to work with you have been inspired by your leadership. You have become endeared to us by reason of your fairness and the foresight with which you have handled the affairs of the College. Therefore, it is my pleasure and privilege, on behalf of your fellow Officers, Regents and Governors of the College, to present to you this Gavel, an enduring token to show our appreciation and the esteem in which we regard you, and to thank you for the admirable way in which you have guided the College through your term of office." (Applause.)

(Dr. Piersol then presented the Gavel to President Barr.)

PRESIDENT BARR: I shall treasure this Gavel as a symbol of a happy year, a year of opportunity to serve the College in which I have great faith and for which we all have high hopes. A realization of the distinction of my predecessors made me approach this year with great humility. Like them, I have done my best to advance the purposes of the College, and at the end of my term, I realize how little I have accomplished and how far it falls short of my estimation of the honor. Anyone who has been an Officer of The American College of Physicians realizes that our management is very sound. Presidents may come and may go, but Mr. Loveland goes on forever. It is fortunate for the College that it is so. He brings to his position the long experience in business of fine judgment and unselfish devotion. All of the arrangements, schedules, agenda, etc., are prepared with such precision that one is not aware of difficulties nor the immense amount of detail which they involve.

To the Committees that carried on the work this year, I wish to express my gratitude, especially to Dr. Reginald Fitz and the Committee on Fellowships and Awards of which he has been Chairman, charged with the selection of six Research Fellowships and the formulation of the James D. Bruce Lectureship and the Alfred Stengel Memorial Award.

The chief task for the President each year is to arrange the Annual Session. This year the arrangements have been made easy and delightful by the extraordinary efficiency and imagination of Dr. LeRoy H. Sloan, the General Chairman, and the fine work which all of his Committees have done over the months preceding this meeting.

In relinquishing the Presidency of the College, it is a pleasure to me to have Dr. Hugh J. Morgan to follow. He has been my friend for many years. I know his sagacity, his dignity, his unfailing kindness, his sense of fitness, and all of you know of his outstanding War record, his eminence as an educator and adviser. The College is, indeed, fortunate to have such a servant to guide its policies during the coming year. I welcome Dr. Morgan. (Applause.)

(President-Elect Dr. Hugh J. Morgan assumed the Chair.)

PRESIDENT MORGAN: I appreciate Dr. Barr's more than generous introduction and your more than cordial reception. I believe I know how Uncle Zeke felt on Judgment Day. During his life Uncle Zeke had been a carousing, lazy fellow and a wicked

man. On Resurrection Day, as he came up from his grave, he read on the tombstone, "Here lies an industrious, temperate man of God." Said Uncle Zeke, "Excuse me, boys, Ah don come up out of de wrong hole."

The chief reason for having Officers at the helm in this College, an educational institution, is to provide personnel for the administration of the business of the College; and, in that spirit, I shall forego this opportunity to express my deep appreciation and will pass on to new business.

The first item to which you must give consideration is certain amendments to the By-Laws which have been approved by the Board of Regents, published in the ANNALS and are now being submitted for adoption by the Masters and Fellows of the College. They will be read by Mr. E. R. Loveland, Executive Secretary.

MR. LOVELAND: The first is an amendment to the By-Laws, Article IV, Section 2, the following paragraph to be added:

"The members of the Board of Governors shall each serve for a term of three years and not more than three consecutive terms."

(Upon motion regularly made, seconded, and carried, it was voted to adopt the above amendment.)

MR. LOVELAND: The following are proposed revisions and amendments of Article V, the insertion of a new Article VI, revision and amendment of old Article VI now becoming Article VII, and with re-numbering of old Articles VII to XIV, inclusive, the new numbers becoming Articles VIII to XV, inclusive:

"ARTICLE V

"Election of Fellows

"*Section 1.* A Fellow of the College shall have met the following qualifications and requirements:

"(*a*) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

"(*b*) He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

"(*c*) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine or an allied specialty at a permanent location for at least three years preceding nomination for Fellowship. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions.

"(*d*) The criteria of eligibility for election to Fellowship are bilateral:

"1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

"2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation,

however, shall not apply to candidates from civilian life who were elected to Associateship prior to April 6, 1940, nor to such candidates from the Army, Navy and Public Health Service who were elected prior to and including April 1, 1944.

"Proposal

"*Section 2.* His name shall be proposed in writing by a Master or Fellow of the College from the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow from the same state, province or territory and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration, or, in special instances, by an officer of the College or by a member of the Board of Regents. His nomination must be accompanied by an adequate written statement made both by the proposer and the seconder, containing all of the above cited qualifications of the candidate. Furthermore, the name of the candidate shall be sent to each Fellow in the candidate's locality with the request for comments as to the candidate's fitness. The proposer must be prepared to add such further information as may be requested by the Committee on Credentials.

"*Section 3.* The credentials of the candidate shall be considered by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

"Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary-General, shall be issued following the Convocation. Acknowledgment of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow, and returned to the Executive Secretary, to be added to the official College roll.

"*Section 4.* Proposals for direct election to Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preëminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following details must be furthermore considered: maturity, national reputation, publications and other contributions to medical science and public welfare. The Committee on Credentials will exercise due discrimination in all proposals for direct election to Fellowship.

"This ruling will not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

"ARTICLE VI

"Election of Masters

"*Section 1.* A special Committee on Masterships will be named by the President. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Master to the Board of Regents for election or rejection.

"ARTICLE VII

"Election of Associates

"*Section 1.* An Associate of the College shall have met the following qualifications and requirements:

"(*a*) He shall hold the degree of M.D., M.B., or M.D., C.M., from a medical school acceptable to the Board of Regents.

"(*b*) After receiving his medical degree, the candidate shall have had at least one year internship in an approved hospital and three years of organized graduate training in internal medicine or allied fields, or its equivalents, approved by the Committee on Credentials and the American Board of Internal Medicine. One year of this graduate training may be spent in the basic sciences.

"(*c*) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions.

"(*d*) If a practitioner, he shall be licensed to practice medicine in his state, province or territory, and shall indicate his purpose to confine his practice to internal medicine or an allied specialty from the date of his application, or be a Medical Officer in the Government Service, either in the United States or the Dominion of Canada, in American or Foreign Service. If not a practitioner, he shall hold an official institutional position in internal medicine, an allied branch of internal medicine or in medical research.

"Proposal

"*Section 2.* His name shall be proposed on the official blank of the College by a Master or Fellow residing in the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow also from the same state, province or territory, and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration; or, in special instances, by an officer of the College or by a member of the Board of Regents.

"*Section 3.* The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

"Successful candidates shall receive at once, from the Board of Regents through the Executive Secretary, an appropriate official notification of their election to Associateship in the College.

"Term of Associateship
and Eligibility for Fellowship

"*Section 4.* Candidates so elected shall be continued as Associates for a term not to exceed five years.

"An Associate will be eligible for election to Fellowship at the end of three years. Upon expiration of this three-year period, he shall be notified in writing by the Committee on Credentials of his eligibility for election to Fellowship during the next two years, provided he has met the requirements necessary for Fellowship within that time. If he is not elected to Fellowship within five years, his Associateship is automatically terminated. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions."

(By motion regularly made, seconded and carried, the above amendments were fully adopted.)

PRESIDENT MORGAN: We shall now hear from the Committee on Nominations, Dr. James J. Waring, Chairman.

DR. WARING: Mr. President, Officers, Fellows and Masters of the College: In accordance with the provisions of the Constitution and By-Laws, the Nominating Committee has placed in nomination and has published in the ANNALS OF INTERNAL MEDICINE the names of nominees for the elective offices as given below and is also placing in nomination the following names for the Board of Regents and the Board of Governors. These nominations do not preclude nominations that may be made from the floor.

"I. Elective Offices:

"President-Elect ..... Dr. Walter W. Palmer, New York, N. Y.
First Vice President ..... Dr. Reginald Fitz, Boston, Mass.
Second Vice President ..... Dr. Francis G. Blake, New Haven, Conn.
Third Vice President ..... Dr. Charles T. Stone, Galveston, Tex."

(President Morgan, after asking for nominations from the floor, of which there were none, called for a vote and the nominees above presented were by resolution regularly elected.)

DR. WARING:

"II. For the Board of Regents, term expiring, 1950:

"Dr. David P. Barr ..... New York, N. Y.
Dr. Alexander M. Burgess ..... Providence, R. I.
Dr. Ernest H. Falconer ..... San Francisco, Calif.
Dr. Cyrus C. Sturgis ..... Ann Arbor, Mich.
Dr. A. B. Brower ..... Dayton, Ohio"

(President Morgan called for nominations from the floor, of which there were none, and by resolution the above nominees were regularly elected.)

DR. WARING:

"III. For the Board of Governors, term expiring, 1950:

"Dr. Arless Arland Blair, Fort Smith ..... ARKANSAS
Dr. Dwight L. Wilbur, San Francisco ..... CALIFORNIA (Northern)
Dr. Benjamin F. Wolverton, Cedar Rapids ..... IOWA
Dr. Edgar Hull, New Orleans ..... LOUISIANA
Dr. Douglas Donald, Detroit ..... MICHIGAN
Dr. Edgar V. Allen, Rochester ..... MINNESOTA
Dr. Ralph A. Kinsella, St. Louis ..... MISSOURI
Dr. Lawrence Parsons, Reno ..... NEVADA
Dr. Harry T. French, Hanover ..... NEW HAMPSHIRE
Dr. George H. Lathrope, Newark ..... NEW JERSEY
Dr. Paul F. Whitaker, Kinston ..... NORTH CAROLINA
Dr. Robert B. Radl, Bismarck ..... NORTH DAKOTA
Dr. Herman A. Lawson, Providence ..... RHODE ISLAND
Dr. Robert Wilson, Jr., Charleston ..... SOUTH CAROLINA
Dr. Ellsworth Lyman Amidon, Burlington ..... VERMONT
Dr. J. Edwin Wood, Jr., Charlottesville ..... VIRGINIA
Dr. George Anderson, Spokane ..... WASHINGTON
Dr. Delivan A. MacGregor, Wheeling ..... WEST VIRGINIA
Dr. Arthur B. Walter, St. John ..... MARITIME PROVINCES
Dr. Arthur T. Henderson, Montreal ..... QUEBEC
Dr. José J. Centurión, Havana ..... CUBA"

These nominations have been respectfully submitted by the Committee on Nominations, George F. Strong, Ralph Kinsella, Asa L. Lincoln, Jonathan Meakins, James J. Waring, Chairman.

(President Morgan asked for nominations from the floor, of which there were none; by resolution the above nominees were regularly elected to the Board of Governors.)

(President Morgan called for President-Elect Dr. Walter W. Palmer to be conducted to the platform, but it was determined that due to delay in air travel, Dr. Palmer had not yet arrived.)*

PRESIDENT MORGAN: I am calling on Dr. Waring to present a resolution of appreciation and thanks to all those who have made this such a wonderful meeting.

DR. WARING: Mr. President and Members of The American College of Physicians: In your names I would like to propose a vote of thanks and keen appreciation to all the following persons who have contributed so greatly to the success of our Scientific Sessions and the ever-to-be-remembered pleasures of this meeting in Chicago:

To our distinguished leader and President, Dr. David P. Barr, for the inspiration of his guidance during the past year, as well as during this meeting; to his Chief of Staff, General Chairman LeRoy H. Sloan, for a magnificent job; to Dr. Howard Wakefield, Chairman of the Chicago Committee on Arrangements; to Dr. Walter L. Palmer, Chairman of the Committee on Clinics; to Dr. Willard O. Thompson, Chairman of the Committee on Panel Discussions; to Dr. Edwin P. Jordan, Chairman of the Committee on Publicity; to Mrs. Thomas J. Coogan, General Chairman of the Committee on Ladies' Entertainment, and all of the lovely ladies on her Committee—to Mrs. LeRoy Sloan, Mrs. Grant Laing, Mrs. Clifford J. Barborka, Mrs. James Hutton, Mrs. Chauncey C. Maher, Mrs. Gilbert H. Marquardt, Mrs. C. Phillip Miller, Mrs. Walter L. Palmer and many others; to the Coöperating Committee of the Chicago Hospitals and other institutions; to civic bodies and local institutions, who opened their doors to our members and their ladies; to the Management of the Palmer House; to Mr. Frank Power of the Chicago Convention Bureau; and last, but not least, to Dr. Clifford J. Barborka, Chairman of the Committee on Entertainment, for bringing "Harvey" to our party; to all these and many others, individually and collectively, our heart-felt thanks again for their generous hospitality in full measure—pressed down and running over.

(There was a standing vote of thanks, in which the members rose and applauded.)

Adjournment—3:00 o'clock.

Attest: E. R. LOVELAND,
Secretary

* Dr. Palmer arrived just at the close of the Business Session and made a short Inaugural Address at the following General Scientific Session.

OBITUARIES

DR WILLIAM EMMETT GARDNER

Dr. William Emmett Gardner, F.A.C.P., died at his home in Louisville, Ky., on April 8, 1947 from coronary artery disease. Dr. Gardner was born in Sonora, Ky., August 24, 1877. He received the degree of Bachelor of Arts from Georgetown College in that state in 1899, and the degree of Doctor of Medicine from the University of Louisville School of Medicine in 1902. He subsequently undertook postgraduate studies in New York, Chicago, Boston, and Cleveland.

Dr. Gardner was a diplomate of the American Board of Psychiatry and Neurology. He held appointments as Psychiatrist and Neurologist in the Norton Memorial, St. Joseph's, Kentucky Baptist, and Louisville General Hospitals. He was also Consultant to the Louisville Neuropathic Sanatorium. He served for a time as a member of the Board of Examiners of the American Psychiatric Association. He returned to the University of Louisville School of Medicine as a member of the teaching staff and attained the position of Clinical Professor of Psychiatry and Head of the Department.

Dr. Gardner was a member of the American Association for the Advancement of Science, the Southern and Kentucky Psychiatric Associations, the Jefferson County Medical Society, Medico-Chirurgical Society of Louisville, Southern Medical Association, Kentucky State Medical Association, and the Louisville Society for Mental Hygiene, as well as a Fellow of the American Medical Association. He was elected a Fellow of the American College of Physicians in 1926.

In reporting Dr. Gardner's death, a Louisville newspaper spoke of him as a "pioneer in introducing modern treatment of mental illness in his native State."

C. W. Dowden, F.A.C.P.,
Governor for Kentucky

DR. THOMAS LAIDLAW SHEARER

On December 13, 1946, the College lost one of its oldest members in the death of Dr. Thomas Laidlaw Shearer, F.A.C.P., of Baltimore, Md. In his passing, we have lost one of the old school; rich in culture as well as medicine.

Dr. Shearer was born February 13, 1859, at Philadelphia, Pa. He received his early education in Baltimore at the Friends Elementary School

and at Johns Hopkins University. For his further education, he went abroad and in 1882 received the degrees of M.A., M.B., C.M., from the University of Edinburgh. The following year he devoted to medical studies in Vienna.

He began his practice of medicine in Baltimore in 1885 in his father's office. During his professional career Dr. Shearer cared for patients in the Women's Hospital, Union Protestant Infirmary, Mercy Hospital, St. Agnes Hospital, Crippled Children's Hospital School. During World War I, he was Acting Medical Examining Officer at Baltimore for the British and Canadian Armies. He also held a reserve commission in the Medical Corps, U. S. Army, as consultant.

Dr. Shearer was a Fellow of the American Medical Association, and a member of the Maryland Academy of Sciences. He was greatly interested in art and was a member of the Municipal Art Society of Baltimore. He also maintained membership in the University of Edinburgh Club of North America.

Dr. Shearer was one of the earliest members of the American College of Physicians, having been elected to Fellowship in 1917.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. HARRY AUGUST BRANDES

Dr. Harry August Brandes, F.A.C.P., died on May 12, 1947, of multiple myeloma at the age of 59 years, after an illness of about seven years. He was born near Granite City, Ill., November 8, 1887, and was graduated from the Washington University School of Medicine, St. Louis, Mo., in 1912. Coming to North Dakota in 1914, he practiced at Hebron and also at Hazen. He served as a medical officer in World War I. Thereafter he became associated with the Quain & Ramstad Clinic of Bismarck, N. D., in the Department of Internal Medicine. He was an Attending Internist to the Bismarck and St. Alexius Hospitals at Bismarck.

He became a Fellow of the American College of Physicians in 1931 and was certified by the American Board of Internal Medicine in 1937.

Dr. Brandes was a physician with keen diagnostic acumen, sound judgment, and personality and ability that won the respect and admiration of his colleagues, and the confidence and esteem of his patients. He served on the North Dakota State Board of Medical Examiners, and as President of the North Dakota State Medical Association for the year 1939–40. His illness began during the latter part of the time that he was President, and he did not return to the practice of medicine thereafter. Dr. Brandes was always intensely interested in civic matters and, even after the onset of his illness,

assisted in many community and state war-time projects to a remarkable degree. He was a member of the Presbyterian Church, Rotary Club, Masonic Lodge, Scottish Rite Bodies, El Zagel Shrine, and the National Sojourners. He was a member of the Advisory Board of DeMolay.

Dr. Brandes served his home community, his state, and the nation with the greatest of ability and diligence. His interest in his fellow man was reflected by the high esteem in which he was held by all those who had the privilege of knowing him. His fortitude during the long period of his final illness was outstanding. He gave much to the world.

ROBERT B. RADL, M.D., F.A.C.P.,
Governor for North Dakota